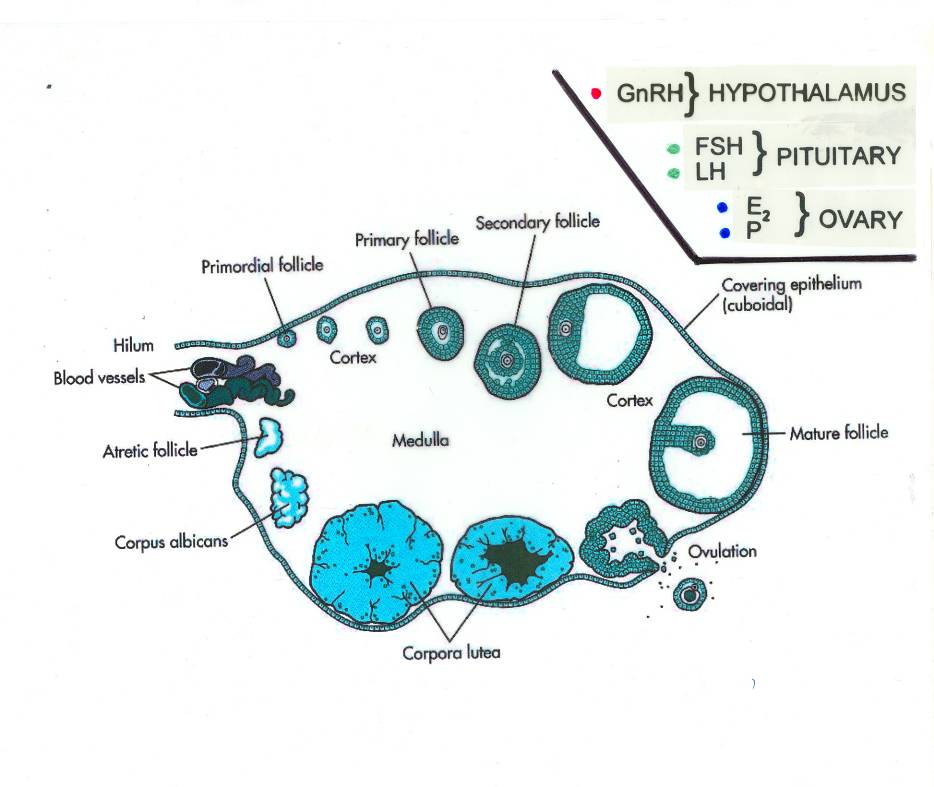
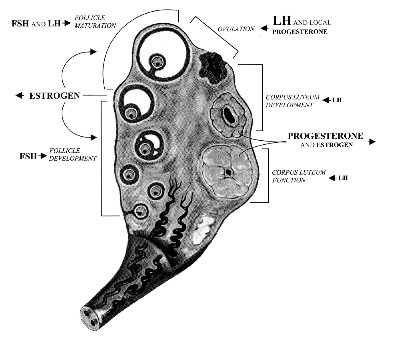
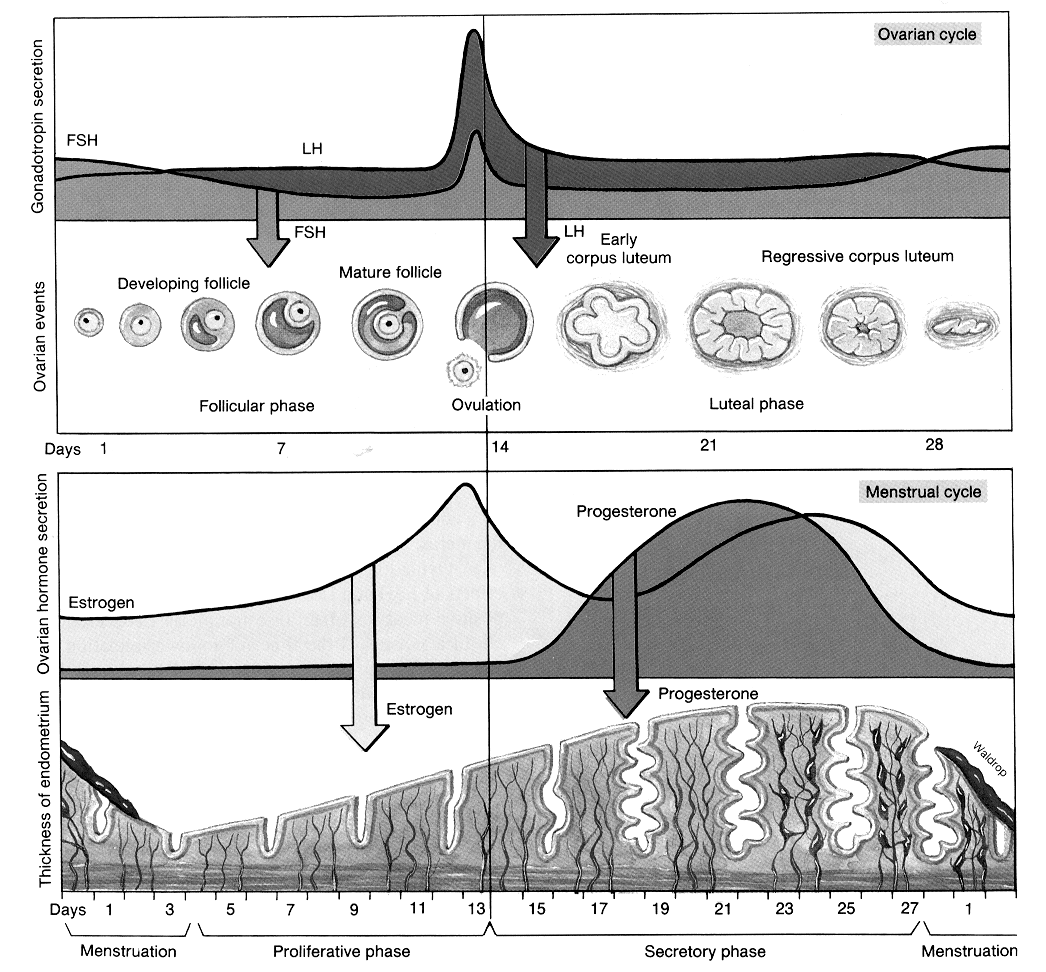
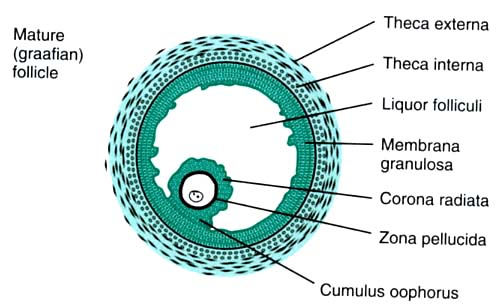
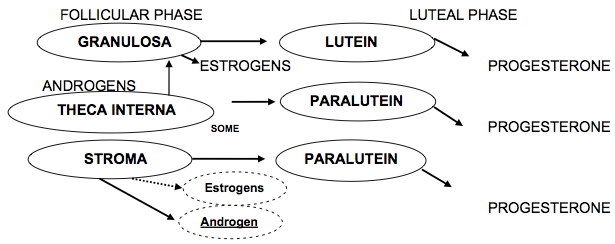
**REPRODUCTIVE PHYSIOLOGY**

**THE FEMALE REPRODUCTIVE TRACT**

* OVARIAN FUNCTIONS
  + Oogenesis—producing eggs
  + Maturation of oocytes
  + Expulsion of the mature oocyte at the time of ovulation
  + Secretion of female sex hormones
* **OVARIAN CHANGES DURING THE MENSTRUAL CYCLE**
  + Throughout this handout,
  + Estrogen = Estradiol = Estrogn 17β (active version of estrogen)= E = E2 unless otherwise noted
  + P= progesterone
  + Primordial follicle are actually present in the fetus. As the follicle grows it begins to have a fluid filled sac called the ANTRUM and within this a cellular peninsulum develops containing the ovum and the OVUM is released at the time of ovulation from the mature follicle. And the remaining tissue that undergoes chemical alterations can become a structure called the CORPORA LUTEUM, which refers to the gross appearance of these structures on the ovary because they look like small yellow bodies. Over time the corpora luteum degenerates and along with it on the surface of the ovary are remaining follicles called ATRETIC FOLLICLES that partially developed but never made it into the point of ovulation and they just degenerated.
  + The Primordial follicles and young follicles can grow a little without hormonal release but to grow substantially they need FSH and will turn into primary follicles
    - FSH will stimulate the production of estrogen
    - Estrogen will then feed forward and stimulate FSH receptors to make more FSH
    - So FSH and estrogen make the follicle grow but you need LH to mature the follicle to the point of ovulation
  + To get a mature follicle to undergo ovulation (THIS IS THE MID POINT OF THE CYCLE) it require 2 things:
    - A little bit of PROGESTERONE and a huge amount of LH, which is known as the Preovulatory LH surge.
  + The Preovulatory LH surge results in a 40-50x increase in the amount of LH over a few hour period. This creates the ovulation.
  + Once ovulation has occurred, the left over cells undergo physical and chemical changes and develop into the corpus luteum
    - The hormone necessary for this to follow is the LH.
    - The main hormone that produced when the corpus luteum is active though is PROGESTERONE but estrogen is also produced
  + After 2 weeks the corpus luteum ends up dying
  + Whenever there is a variation in the length of the menstrual cycle. The LUTEAL PHASE is pretty much always 14 days but the FOLLICULAR PHASE is the one that varies. Most cycles last 28 days but they vary. If you have a 44 day cycle the follicular phase is the 30 day one. We will look at why this is the phase that varies.
* OVARIAN CYCLE AND MENTRUAL CYCLE
  + FOLLICULAR PHASE OF THE OVARY
    - AKA PROLIFERATING PHASE OF THE ENDOMETRIUM
    - This part of the cycle is what varies in women.
    - Estrogen levels ↑ slowly
  + Ovulation—dramatic rise in both FSH and LH
  + LUTEAL PHASE OF THE OVARY
    - AKA SECRETORY PHASE OF THE ENDOMETRIUM
    - As you enter the luteal phase FSH and LH are suppressed because you elevated levels of progesterone and estrogen producing negative feedback
    - Estrogen important for building the endometrium
    - Progesterone present in the luteal phase is the gland worker preparing for implantation
    - As the corpus luteum begins to degenerate progesterone and estrogen begin to drop off and the result is that the endometrium doesn't have the hormones it did have so it begins to slough off and this is what appears as the vaginal flow of the menses
    - 14-16 days and THIS DOES NOT CHANGE.
* OOCYTES (eggs)
  + 7 million formed
  + 2 million at birth
    - Meiosis incomplete
    - They remain in the dliplotene phase of prophase 1 of meiosis I and it remains that way until puberty
  + 300,000 at puberty
  + 450 ovulated across adulthood
    - Meiosis completed at ovulation/fertilization
    - At the time of ovulation, the next phase of meiosis occurs where the polar body is extruded and at the time of fertilization the next polar body is extruded
  + COMPONENTS OF THE MATURE OVARIAN FOLLICLE
    - ANTRUM: fluid filled sphere that contains liquor folliculi
    - Theca Externa-- not a source of hormones
    - Theca Interna-- also a source of hormones
    - Membrana granulosa-- source of the hormones
    - Corona Radiata—surrounds the zona pellucida
    - Zona pellucida-- protein layer that is acellular and important for fertilization - the black line
    - Cumlus oophorus-- at the base of the zona radiata

**CELL LINES AND HORMONE SOURCES IN THE OVARY**

* 2 different types of cells within the same structure but they are derived from each other. So the cells present in the Luteal Phase are derived from the cells in the Follicular phase of the cycle.
* FOLLICULAR PHASE
  + We have Granulosa cells and Theca interna cells and Stromal Tissue
    - Granulosa source of estrogens
    - Theca interna cells work in conjunction with the granulosa cells to produce the estrogens by providing the androgens to the granulosa cells
* LUTEAL PHASE-- The cells in the luteal phase come from the cells in the follicular phase.
  + The conversion that occurs after ovulation to produce the corpus luteum is the conversion of the granulosa cells 🡪 Leutein cells; and the Theca interna cells 🡪 Paralutein cells
    - provide androgens to the granulosa cells
  + Stroma🡪 small amt of estrogens & androgens but less than the theca interna
    - Small amount of the Stromal cells of the interstitium of the ovary can get converted into Paralutein cells
* There is a "cell population" in the ovary. So that means that at any given time there are a certain amount of cells that are granulosa and theca interna even in the corpus luteum. Also some portion of cells are lutein and paralutein cells even within the follicular phase before most of them convert. As a matter of fact, it's the small portion of cells that convert that are more sensitive to hormonal stimulation that would convert them and these form the progesterone that is necessary in the follicle BEFORE ovulation and the corpus luteum forms.

**ANDROGEN ROLES IN FEMALE**

* Estrogen precursor in ovary and brain
* Puberty—onset of puberty
* Libido—primary stimulus for sex drive
* Anabolic—So when they're present they function in an anabolic fxn as well as in the reproductive tract
* Excess symptomatic in some diseases—similar to congenital adrenal hyperplasia (CAH) when we were talking about the adrenal

**ANDROGEN SOURCES IN THE FEMALE (FOLLICULAR PHASE)**

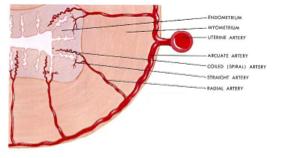
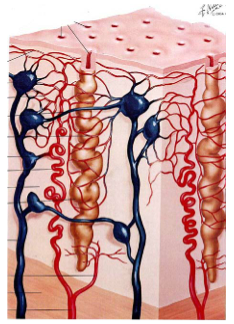
|  |  |  |
| --- | --- | --- |
|  | AVERAGE % CONTRIBUTION | |
| TISSUE | ANDROSTENEDIONE—weaker androgen | TESTOSTERONE |
| OVARY | 60 | 45 |
| ADRENAL | 40 | 55 |

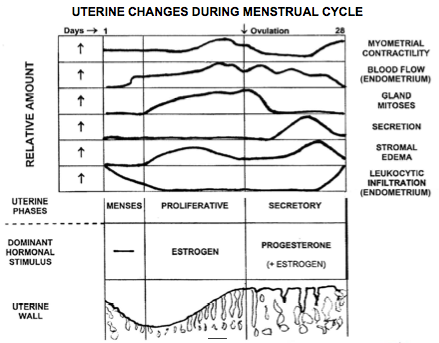
* Most androstenedione is converted to testosterone in the periphery.
* Plasma testosterone levels in women are 6-8% of those in men, and 60% of this plasma T is from peripheral conversion of androstenedione.
* Plasma levels of proteins that specifically bind androgens (TeBG) are 2-3-fold higher in women than in men.
  + There is less testosterone present and less FREE testosterone present in the female

**FUNCTIONS OF THE UTERUS**

* Prepare for implantation
* Nourish the conceptus
* Expel the fetus

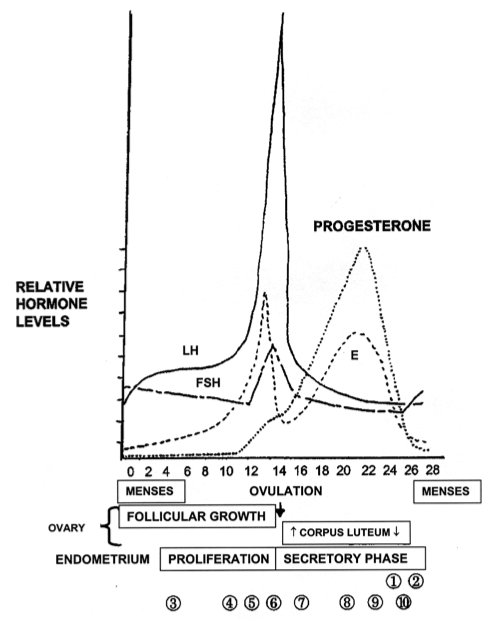
**UTERINE CHANGES DURING MENSTRUAL CYCLE**

* 
* **Note:** E increases uterine P receptors (i.e., P performs best in an E-primed uterus)
  + Endometrium (inner layer) goes dramatic changes in thickness due to hormones. The primary changes involve the development of arterioles and venules that become much more well developed as it proliferates under the role of estrogen. The growth of the glands that are actually the nutrient source after implantation is mostly due to estrogen. Once ovulation occurs and the corpus luteum is formed these glands act as secretory units providing nutrients which are necessary.
  + Myometrium (outer layer) does response to sex hormones estrogen and progesterone but not by changes in it's size but in its contractility. Estrogen causes contractility and progesterone usually prevents that.



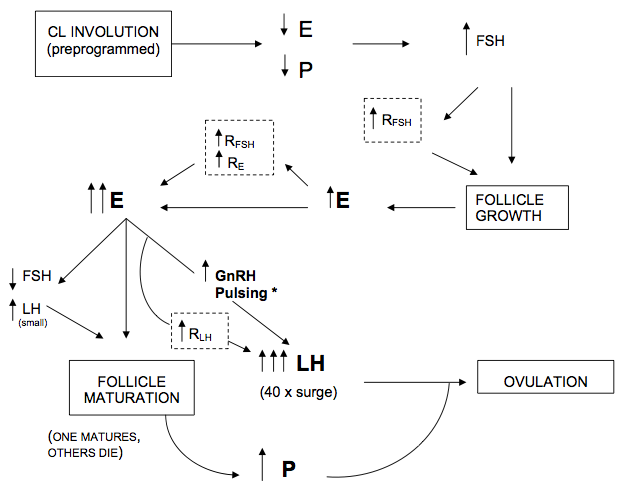
* Myometrium responds to the Increasing amounts of estrogen by causing ↑ contractility.
* Then when ↑ progesterone inhibits that and later when there is more estrogen than progesterone it causes contractility again.
* Once you get closer to onset of menses the estrogen:progesterone ratio is ↑ in the favor of estrogen so you get ↑ contractility

**CIRCULATING HORMONE LEVELS DURING OVARIAN AND ENDOMETRIAL EVENTS IN THE HUMAN MENSTRUAL CYCLE.**

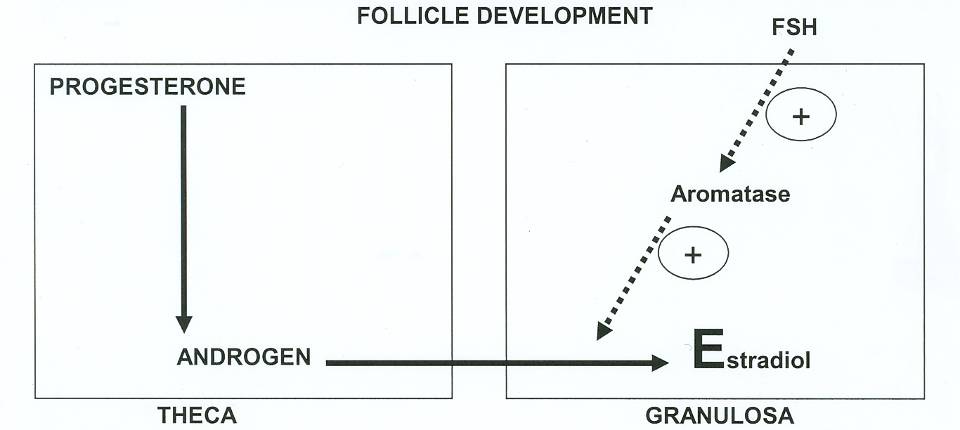
* MUST BE ABLE TO INTEGRATE--Ovarian function, Blood levels of hormones, and Endometrial function
* Ovulation occurs when there is an ↑ in LH there is also a rise in FSH and before this there is a rise in estrogen.
* There is little progesterone in the follicular phase of the cycle but it dominates the luteal phase.
* Start point—drop in estrogen and progesterone🡪 leading to slight drop in negative feedback on FSH leading to ↑ FSH
* This ↑ in FSH just before the onset of menses is what starts the next round of follicles growing for the next menstrual cycle. And as the follicles grow the FSH will eventually taper off gradually leading to and ↑ in LH which is significant just before the time of ovulation
* This increase in LH and decrease in FSH reflects the differing sensitivity in the pituitary gland to the singular hormone that stimulates both of these hormones🡪 GnRH
  + So GnRH stimulates FSH and LH but it can do so SELECTIVELY which is why you can get ↑ LH and ↓ FSH at the same time
* Estrogen levels are starting to rise bc the FSH is stimulating the follicles to produce estrogen. It increases fairly slowly for about the first 10 days and then the last days it increases dramatically
* After estrogen peaks and after the LH surge, the estrogen falls dramatically for a few days—this is result of the follicle is ruptured and egg is released so the remaining tissue must get back on tract to ↑ production of estrogen and progesterone
* The estrogen rise causes the dramatic LH peak (LH surge is super important in ovulation)
  + There is also an FSH rise that corresponds to the LH surge but this is actually an overlap effect of the GnRH stimulating the LH—the FSH it plays no significant role in ovulation
* The follicle undergoes changes to produce the corpus luteum and then estrogen and progesterone go up and are active for 11-12 days in a 28 day cycle.
* A small percentage of granulosa cells and theca interna cells that convert into lutein and paralutein cells and begin to produce progesterone before the progesterone peak so they are responsible for the role of that progesterone plays in ensuring ovulation will occur (along with LH)
* Receptor competency and this process🡪Start off with the corpus luteum involuting so estrogen and progesterone go down. This results in increase FSH by loss of negative feedback. We end up with follicles beginning to grow. This is associated with an ↑ in FSH receptors stimulated by FSH itself. FSH itself creates more FSH receptors and this contributes then to the competency of the tissue to respond to FSH. This growth can only go so far without estrogen but it starts making estrogen and estrogen creates more receptors for itself as well as FSH. It's a feed-forward response. This is what creates the rapid rise in estrogen 1-2 days before ovulation. This rapid ↑ in estrogen actually inhibits FSH. There are other things coming out of the follicle which also inhibit FSH. There is also small ↑ of LH (remember that FSH and LH can be effected differently despite the presence of GnRH). In this case you have a decrease in FSH and a small increase in LH and an increase in estrogen. One of the things that estrogen does is ↑ the receptors for LH and also activates a protein in the hypothalamus which and along with other things that ↑ GnRH activity. It increases an increase pulsing pattern of the GnRH and due to this and the ↑ LH receptors you end up getting a 40- 50 fold surge in LH within a few hours.
* Once again you have the follicle maturation due to the small amount of LH present before ovulation and there are increasing progesterone (due to the paralutein and lutein cells which were converted from the granulosa, theca interna, and stromal cells) so you end up getting ovulation.
* In looking at the details of the LH surge it is clearly a positive feedback event b/c of the rapidly rising estrogen that triggers GnRH and LH release. You have high levels of estrogen and you are getting ↑ LH and GnRH which is counterintuitive to the classical negative feedback pattern. Notice that this is an acute activity over a small period of time. It also requires optimum input from other parts of the CNS- The limbic system and all the other tracks to the hypothalamus come into play here. If there are events like anxiety, stress, etc that interfere with the optimal CNS activity to occur you won't get the normal LH surge and ovulation b/c it will affect the making of GnRH. You need optimum neural input and two other things: 1. The acute inhibition of GABA and βendorphin yielding GnRH pulsing changes 2. A protein made in the anterior portion of the hypothalamus that is called kisspeptin (activator of the GnRH producing cells which are in the arcuate nucleus)
* In order to get the LH surge to occur you need to get a shift in the GnRH pulsing. So the kisspeptin activate the GnRH cells and the GABA inhibition and β endorphin inhibition to allow GnRH pulsing to occur and then you have a shift in the pulsing from the high frequency low amplitude pattern so a low frequency high amplitude type of pulsing🡪 resulting in the trigger for the increasing GnRH to allow for the LH surge

**EVENTS OF THE MENSTRUAL CYCLE**

* The hormonal changes of the menstrual cycles in women are illustrated in the figure on the previous page. The events are listed below. The circled numbers in the diagram show when the various events occur.
  + As the corpus luteum involutes, a precipitous fall in circulating levels of both estrogen (E) and progesterone (P).
  + In consequence, there is a small but constant increase in FSH, which may persist through the menses. FSH levels then gradually fall until near ovulation.
  + The initial rise in FSH concentration stimulates several follicles to begin to develop, partly via induction of cyclin D2 (a regulator of the cell cycle clock). After a few days, one of these, usually the most developed one begins to mature rapidly, while the others begin to involute. The "chosen" follicle secretes E locally, which increases its sensitivity to gonadotropin stimulation, while sensitivity of the other follicles diminishes. Increased E production by the granulosa cells derives from FSH stimulation of aromatase enzyme which converted androgens (coming from thecal cells) into E. The E induces both FSH and E receptors in this follicle, further increasing responsiveness in a feed- forward fashion. Although numerous follicles grow in each cycle, only one reaches full growth and matures, due to that follicle having had the greatest concentration of FSH receptors and E receptors (it is the follicle which achieved greatest growth without degeneration in the previous cycle). The other follicles of similar growth undergo a degenerative process called atresia, defined as the apoptotic involution of partially grown follicles. Atresia occurs at all stages of follicular antral development. Several agents play a significant role in the atretic process, and these atretogenic factors, in order of importance, are: A) TNF, B) androgens, C) fas-activating ligand and D) interleukin-6.
  + In the week before ovulation, the maturing follicle produces large amount of E. This is enabled by the process described in step 3 and by LH stimulation of androgen production in thecal cells. The latter insures a supply of androgen for the aromatization occurring in the granulosa cells.
  + P synthesis (by early-convert granulosa → lutein cells) is stimulated by the rise in LH that occurs just before the midcycle LH surge. P is essential for the synthesis of enzymes that are responsible for locally thinning the follicular wall through which the ovum will be extruded.
  + Ovulation - The Focal Event in the Cycle.
    - The ovulatory surge of LH and FSH is triggered by a positive feedback effect of rapidly increasing estradiol above a specific threshold for 2 days. This positive feedback effect is at both pituitary and hypothalamic levels. In the latter, E stimulates a peptide (kisspeptin) in the anteroventral periventricular (AVPV) region, which signals the arcuate nucleus to release GnRH.The pituitary gland, appropriately primed by the preceding pattern of ovarian steroid exposure, now responds to repetitive GnRH pulses in exaggerated fashion. The frequency and amplitude of pulsing is regulated by acute shifts in hypothalamic GABA and β-endorphin activity. Proper pulsing results in a large surge release of LH. FSH is also released because GnRH stimulates both FSH and LH, but the FSH plays no role in the ovulation process. If the rising E concentration before ovulation is neutralized with antiestrogen antibody, the midcycle gonadotropin surge does not occur, and ovulation is blocked.  Because of the myriad neural connections of many portions of the nervous system with the hypothalamus, the activity of the hypothalamic-pituitary system can readily be influenced. Nervous input from other parts of the CNS must be optimum for the hypothalamic-pituitary system to respond appropriately to E. *For example: Stress and anxiety can retard or advance ovulation by several days or even prevent it.*
    - Ovulation occurs approximately 12 hours after the LH surge via the multicomponent mechanism listed below:
      * 1)  LH neutralizes the action of oocyte maturation inhibitor (OMI), allowing completion of meiosis.
      * 2)  Stimulation of P synthesis by LH enhances proteolytic enzyme activity, which loosens the wall and increases distensibility of the follicle.
      * 3)  Local synthesis of prostaglandins, some of which are required for follicular rupture, greatly increases.
    - To enable the above processes requires the functional integrity of the following 3 effector proteins, the expression of which are activated by LH via a transcription factor known as C/EBP:
      * 1)  P receptor (enabling P action)
      * 2)  Cyclooxygenase (enabling prostaglandin synthesis)
      * 3)  Cyclin D2 (a cell cycle activator)
  + During the immediate postovulatory period, there is a transitory drop in circulating steroids, and the ruptured follicle becomes filled with luteal cells, which are yellow and lipid-laden. As these cells proliferate into the cavity, new blood vessels form. The new structure is called the corpus luteum. The enzymatic "emphasis" in these cells is such that they produce large amounts of P, as well as E, under the influences of LH.
  + The high circulating levels of E and P during the time of corpus luteum function (14 days) inhibit the release of gonadotropins.
  + In some species, a luteolytic substance produced by the uterus is responsible for involution of the corpus luteum. In primates there is no evidence that such a substance exists, since the corpus luteum degenerates even if the uterus is removed. The primate corpus luteum may be pre- programmed to degenerate at a fixed time without the necessity of external signals. It appears that prostaglandin F2 is involved in luteolysis.
  + When the corpus luteum degenerates, there is a sharp decrease in circulating E and P levels. As a result of the steroid decrease:
    - There is a selective increase in serum FSH concentration, which initiates a new wave of follicle maturation.
    - The secretory endometrium undergoes hemorrhagic and degenerative changes, which culminate in the bleeding and discharge that constitutes the menstrual flow. At the time of endometrial sloughing, there is marked constriction of the arterioles and a slowing of circulation, with extravasation and pooling of blood in the stromal layer. The submucosal blood pools coalesce, and the superficial layers of endometrium, leukocytes and mucus are shed as menstrual discharge. The blood of this discharge does not clot readily, and it may vary in amount from 20 to 200 ml for a single menses. The flow lasts 3-7 days in 95% of women. Only about 20% of the endometrium actually sloughs in a given cycle. The remaining 80% of tissue undergoes remodeling during the next cycle.
  + NOTE: a diagram of the steps in the ovarian cycle is provided on the next page as an additional perspective on this complex sequence of activities.

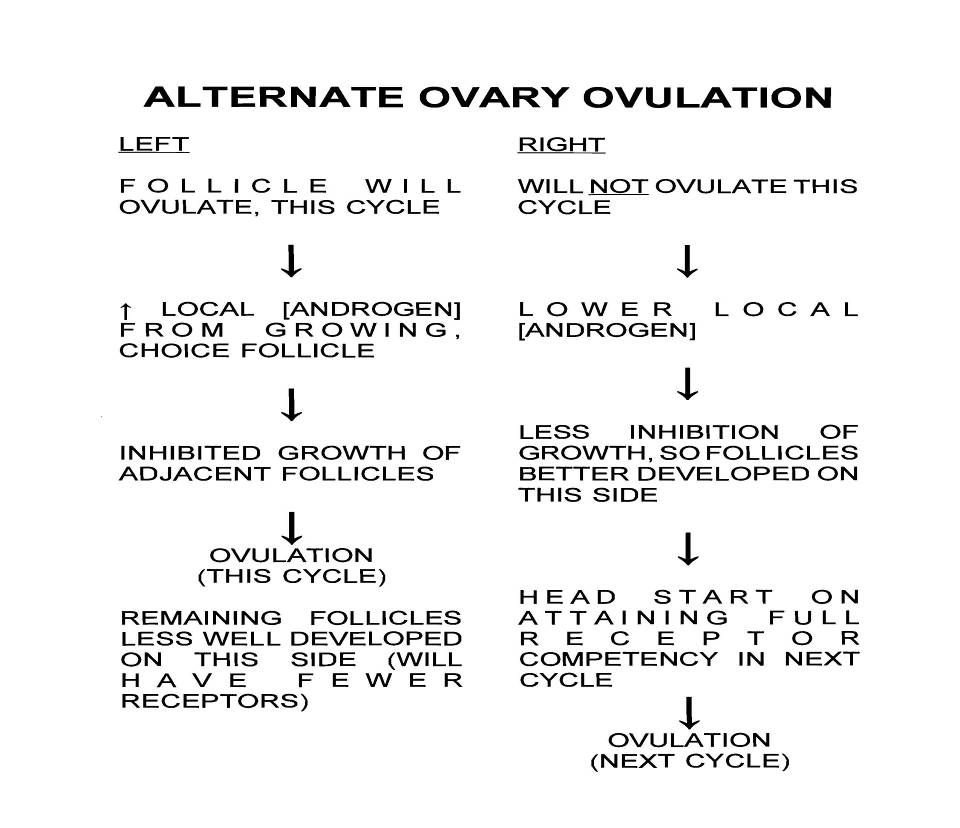


* + This is a positive feedback (feed-forward) event
  + requires optimum CNS input (e.g., stress and anxiety can advance/retard  process several days).
  + GnRH increases FSH and LH, but only the LH is important for ovulation.

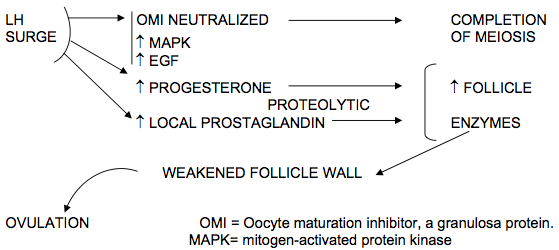


* Looking at the follicles due to LH. The theca interna cells are taking progesterone that is present and converts it into androgens and shuttles it from the interna to the granulosa. In the presence of aromatase enzymes it converts the androgen into estradiol.

**ATRESIA OF OVARIAN FOLLICLES**

* DEFINITION: Apoptotic involution of partially grown follicles
* Occurs at all stages of follicular antral development
* Numerous follicles grow in each cycle.
  + Only one reaches full growth and maturity, due to greatest FSH-R and E-R competency.
  + The others become atretic.
  + Normally there are 10-20 follicles that grow partially in each cycle but only one will reach growth and maturity. There is always 1 follicle that has a better competency for FSH in a given cycle. This one has the best chance of growing and the others become atretic
* Important participants in atretic process, i.e., atretogenic factors, include (in order of importance):
  + TNFα
  + Androgens
  + *Fas*-activating ligand –Fas ia a death promoting agent and the ligand activates it to allow for it to do its job
  + Interleukin-6
* Generally the ovaries ovulate alternately from month to month, since the ovary ovulating in one month has less developed follicles (repressed) than the other ovary.
  + The rule of thumb is 1 baby per pregnancy. This appears to be because the ovaries alternate from one cycle to the next. This is because the follicle that's ovulating has ↑ local androgens and that suppresses growth of adjacent follicles within that ovary. In the other ovary there is ↓ in local androgen so less inhibition of growth so the follicles will be better developed on that side so the less well developed follicles on the side that has the follicle which was chosen to grow for ovulation will not become the follicles that are chosen for the next ovulation cycle because the opposite ovary follicles are better developed and more competency for growth.
  + What happens when 1 ovary is removed? It still goes on in the remaining ovary.

**POST LH-SURGE EVENTS LEADING TO OVULATION**



* Oocyte maturation inhibitor (OMI) produced in granulosa layer; MAPK— mitogen activated protein kinase; and EGF
  + These work to complete meiosis. At the time of ovulation the first polar body is extruded. You need these agents to do this.
* ↑ in local PG’s within the follicle
* The follicle wall becomes weak and the egg just comes out. It doesn't blow out…It just kinda opens up and the egg comes out its not under pressure. The wall stretches and comes out as the follicular fluid expands.

**CONTROL OF CORPUS LUTEUM (CL)**

* Formation
  + Due to LH-induced conversion of follicular cells to lutein cells
  + The secretory phase depends on getting a huge percentage converted in a few days
* Secretion
  + Due to increasing number of lutein cells
  + Small amount of LH needed for maintenance of the CL but it LH wont prolong the life span of the CL (only thing that will prolong its life span is HCG)
* Breakdown (luteolysis)
  + Lifespan normally and reliably 14-16 days
  + Possibly preprogrammed
  + ↑ E/LH ratio and ↑ PGF2α may facilitate breakdown.
  + As long as you have LH present to maintain it, it will start undergoing these changes on its own. ↑ in ratio of estrogen: LH or ↑ in PGF2α can facilitate the breakdown so it's 14-16 days.
    - These are the only thing that can alter that besides HCG hormones
* Secretion in pregnancy
  + HCG from developing chorion (mostly LH-like, some FSH-like) 🡨similar in structure and activity to LH than to FSH
    - Prevents luteolysis
    - Prolongs steroid production until placenta takes over.
      * It's present for a number of weeks after it would normally degenerate and this is because of the presence of HCG
    - Then CL degenerates

**MENSES**

* E & P from CL sustain endometrium
* E & P Withdrawal (When CL Degenerates) leads to hemorrhagic and degenerative change in endometrium.
  + The blood supply to the tissue is reduced and the tissue becomes hypoxic and this really starts the partial sloughing of the endometrium (the whole endometrium does not slough)
* Partial Sloughing Of Endometrium Occurs (Menses)
* Menstrual Flow Contains
  + Endometrial Cells
  + Leukocytes
  + Blood -- significant amount
  + Mucus
* Menstrual Flow (variable)
  + 20-200 Ml. Volume
  + 3-7 Days Long
  + Once a menstrual cycle has become established the menses cycle is pretty constant for a given individual.
* 80% Of endometrium is retained and remodeled for the next cycle.

**ENDOMETRIOSIS**

* Endometrial tissue inappropriately back-migrates to uterine tubes (in the fallopian tubes, sometimes attached to the ovaries), ovaries and sometimes inside the peritoneal cavity
* Can proliferate due to cyclic E and P of ovarian cycle
  + It can even grow a bit more with each cycle and eventually a sizable amount of tissue
* Is benign tissue, but is found incidentally in 20% of gynecologic surgeries
  + Not uncommon.
* Common symptoms are pelvic pain of varying degrees and eventual infertility
* Treatment by hormone suppression or eventual surgical removal of the tissue (severe cases may require reproductive tract removal)
  + Sometimes this is not a simple procedure and a hysterectomy must be performed to fix this.
  + It can be painful and debilitating and should not be ignored.

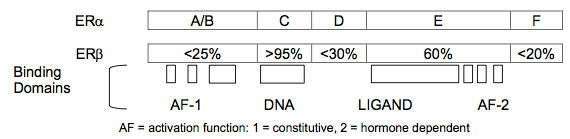
**EFFECTS OF ESTROGEN AND PROGESTERONE ON UTERINE TUBES, CERVIX AND VAGINA**

|  |  |  |
| --- | --- | --- |
| **TISSUE** | **ESTROGEN—**predominates in the  follicular phase | **PROGESTERONE—**predominates in the luteal phase |
| Uterine tubes— aka fallopian tubes | ↑ contractility  of the SM  ↑ secretion (lubrication)\*  ↑ ciliated cells— in the number of ciliated cells; important for movement of egg and the joining of the egg and the sperm | ↓ contractility  ↓ secretion (lubrication)\*  ↓ ciliated cells |
| Cervix (cervical mucous) | ↑ volume  ↓ viscosity  ↑ pH  ↑ [Na+]—Na can be used to see which phase you’re in. If there is a firming pattern on a slide it means lots of sodium and that ovulation has occurred. | ↓ volume  ↑ viscosity  ↓pH  ↓ [Na+]  \*\*If you look at the effects. When Progesterone is present than the chance of getting successful sperm transport and survival is low—b/c ↓ volume, ↑ viscosity, they like alkaline environment so ↓ pH is bad for them |
| Vagina | ↑ cornification (maturation of stratified squamous epithelium)  ↓ sloughing of epithelium  ↓ pH— Advantage of this is that it's not as hospitable to bacteria. Two things that cause ↓ pH:   * Estrogen facilitates protein transport from the vaginal epithelial cell and into the lumen * Estrogen increases the storage of glycogen which can serve as a bacterial substrate for the lactobacilli which create a lower pH | ↓ cornification (maturation)  ↑ sloughing of epithelium (immature and cornified)  ↑ pH |

* \* = This is different from the nutrient secretion stimulated by progesterone in the endometrium.

**ESTROGEN RECEPTORS**

* E has 2 receptors ERα (classical) and ERβ (1996).
  + There are 2 receptors for estrogen.
* Domains within the ER and % homology of β with α .



* + - The % are percentage of what they have in common
* α *vs.* β
  + ERα predominates in uterus, mammary gland, testes and non-reproductive tissues.
  + ERβ predominates in ovary and prostate.
    - There are estrogen receptors in the male!
* In some tissues (e.g., ovary) both α and β receptors required for normalcy.
  + So anything that influences relative amounts of the receptors competency can influence the biological responsiveness to the estrogen that's present
* Studies with knockout genes (mostly in mice) are enhancing picture of differential roles of ERα and ERβ .

**E2 AND P RELATIONSHIPS**

* E effects usually dominate
* P usually antagonizes E effects, but also E increases P receptors (a feedback loop?)
  + Provides a sort of feedback to prevent estrogen effects from being too excessive
* The E/P ratio can be as important as E or P alone in overall effect.
  + At the end of the luteal phase (end of this phase you have more estrogen to progesterone domination)
  + Oral contraceptives ratio is important in the effectiveness.
  + Onset of partrition.

**NON-REPRODUCTIVE, PHYSIOLOGICAL EFFECTS OF ESTROGEN**

* Estrogen is the main hormone that has effects outside of the reproductive tract. Progesterone does have some, but not even comparable to that of estrogen.
* INTEGUMENT
  + Prevents wrinkles and oiliness of skin
  + Prevents thinning of skin
    - His next door neighbor was 102 y/o and you could see through her skin and it was due to age and thinning of the skin
* SKELETON
  + Female pelvic arrangement (different from male)
  + Prevents calcium loss from bone
    - Reason why in menopause osteoporosis in women.
  + Inhibits growth of long bones (male tends to be taller than women)
    - Also effects epophaseal closure so women are shorter.
* METABOLISM
  + ↑ Deposition of subcutaneous fat
  + ↑ Protein anabolism
  + General weight gain
  + ↓ Glucose tolerance
  + ↓ Serum cholesterol
* GI TRACT-- So these are common effects of contraceptives containing estrogen (pharmacological estrogen)
  + Nausea
  + Vomiting
  + Bloating
* BLOOD—The first 4 of these must be addressed before you give someone oral contraceptives.
  + ↑ Fibrinogen
  + ↑ Platelet agglutination
  + ↓ Clotting time
  + ↑ Thromboembolism\*\*
  + ↑ Binding proteins in plasma—can produce alterations of the hormones in a pregnant individual
* RENAL-ELECTROLYTE—So some women get edema from oral contraceptives.
  + ↑ Water retention –edema
  + ↑ Na+ retention
* CNS— The major symptoms of PMS are associated with these.
  + Altered thermoregulation
  + ↑ Excitability of neurons – Lowers neuronal threshold for firing.
  + ↑ Emotionality and irritability
  + Depressed mood
  + Headaches
  + Altered in libido

**CIRCUMSTANCES CLEARLY EVIDENCING ESTROGEN-RELATED EFFECTS**

* Puberty - adolescence
* Menopause - climacteric
* Premenstrual syndrome (PMS)
* Oral contraceptive side effects

**NON-REPRODUCTIVE, PHYSIOLOGICAL EFFECTS OF PROGESTERONE**

* Thermogenic (via action on hypothalamic thermoregulatory centers)
  + Direct neuronal effect on the hypothalamus
* Antinatriuretic (via renin release)
  + Promote Water retention (just like estrogen) and breast tenderness increases later in the menstrual cycle in the luteal phase especially when estrogen and progesterone are high.
* ↓ Excitability of neurons (euphoric in high dose) --↑ neuronal threshholds
  + Usually women in the 2nd half of pregnancy usually have a good state of mind b/c highest progesterone levels
* Hyperventilation (↑ PCO2 sensitivity)
  + Can stimulate hyperventilation.

**PREMENSTRUAL SYNDROME (PMS)**

* A syndrome of varied physical and emotional distresses occurring late in the luteal phase of the menstrual cycle (sometimes into menstruation, or throughout luteal phase).
  + THESE NEVER OCCUR IN THE FOLLICULAR PHASE of the cycle. If it does this can't be diagnosed as PMS.
* SYMPTOMS INCLUDE: (All due to alterations in the CNS.)
  + MOST COMMON
    - Anxiety
    - Depression
    - Headache
    - Spontaneous crying
  + COMMON
    - Fatigue, lethargy
    - Need for more sleep
    - Food cravings
    - Muscle tension
    - Breast swelling and pain
    - Edema
    - Abdominal distention
    - Pimples
    - Constipation
* Etiology - unknown but likely candidates are:
  + Relative excess of E or hypersensitivity to E (Their tissues have high receptors of estrogen)
  + Relative deficiency of P
    - Ration of E to P plays an important role in PMS
    - CNS symptoms are due to low P/↓ P competency🡪 ↓ GABA receptors 🡪 ↑ anxiety
* Characteristics of Symptomatology
  + Occurs in about 30% of women, but only 1/3 of those seek treatment.
    - This has increased in the past 15 yeas.
  + An individual may have few to most of these symptoms. (CNS ones are most common)
  + If these symptoms occur in follicular phase of cycle, it is not PMS.
  + Temporal pattern-- Varies from individual to individual.
    - Onset week before menses
    - Improves 1-2 days pre-menses
    - Ends 1-3 days post menses
      * IN some women can last a couple of weeks.
  + Symptomatology is classified as
    - Mild
    - moderate
    - Severe (truly  Incapacitating)
    - Severest form (<10% of women) is premenstrual dysphoric disorder (PMDD).
      * They are completely useless during this time.
* Treatment is individual-specific and is usually focused on particular symptoms. Treatment can  include:
  + Diet and exercise
  + Relaxation-training – Yoga or biofeedback
  + Progesterone therapy
  + Anti-inflammatory drugs
  + Serotonin-enhancing antidepressants (e.g., Prozac®)
  + Anxiolytic drugs—like benzo’s

**POLYCYSTIC OVARY SYNDROME (PCOS)**

* Introduction
  + Polycystic ovary syndrome, PCOS, was originally discovered and described as a syndrome by Stein and Leventhal (Stein-Leventhal syndrome). It is presently called PCOS or polycystic ovarian disease (PCOD).
  + Most common endocrinopathy in women
  + Most common cause of anovulatory infertility
* Symptomatology
  + General
    - PCOS is a symptom complex associated with polycystic ovaries and characterized in >50% of cases by:
      * Oligomenorrhea (infrequent menstrual flow (<9 menstrual periods a year) or amenorrhea (absence of menses for greater than 3 months))
      * Anovulation (absence of ovulation)
      * Obesity (rising incidence of PCOS related to rising obesity)
      * Hirsutism (abnormal hairiness in a male-type distribution) -- facial hair and hair on the sternum etc.
  + Physical
    - White, smooth, sclerotic ovaries with thickened capsule
    - Thecal cell hyperplasia
      * The theca interna and theca externa are hyperplastic.
    - Chaotic follicle growth – Many more follicles grow.
    - Numerous atretic follicles (not really cysts)
  + Onset of chronic or frequent anovulation
    - Typical pubertal onset is normal-age menarche followed by a year or two of menstruation with periods  then becoming irregular and ceasing.
    - Associated with increased risk of endometrial and breast cancer
  + Onset of hirsutism
    - typically pubertal -- in adolescence
    - can be in adulthood
      * Especially as the obesity precipitates it.
* Etiology of PCOS
  + Not ovarian
  + Most likely related to hyperinsulinemia
    - All PCOS patients are hyperinsulinemic (this is diagnostic for PCOS)
    - Majority of PCOS patients are obese
      * Obestity and PCOS
        + PCOS and obesity are increasing in USA

Frequent anovulatory cycles yield

↑ endometrial cancer risk

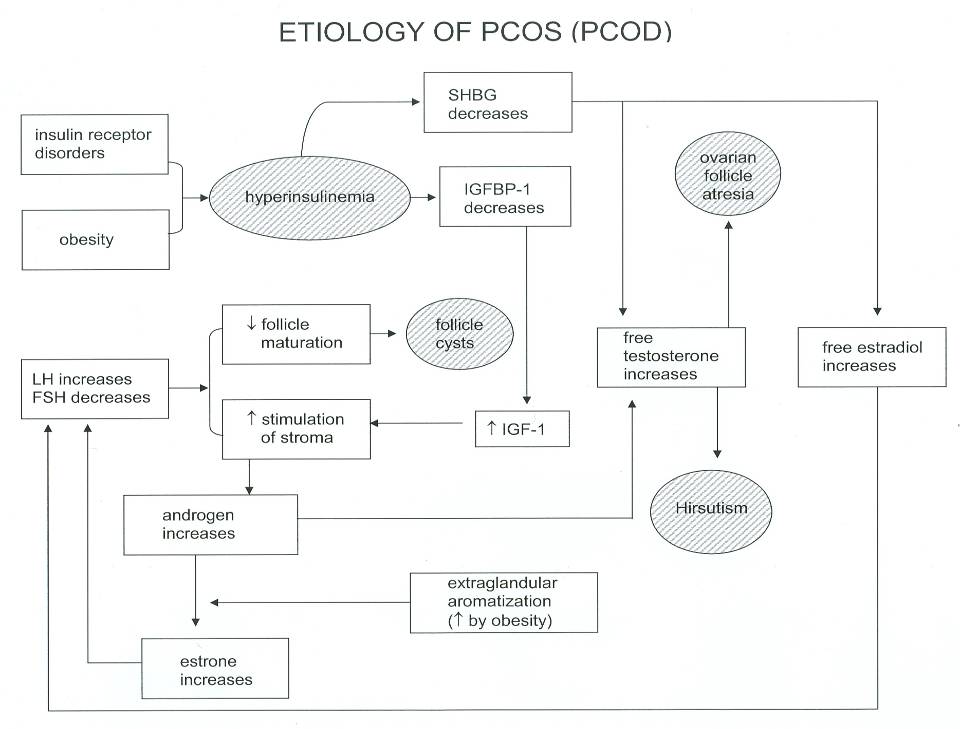
↑ breast cancer risk

If the disorder occurs it must be dealt with.

* + - * + Obesity is associated with

Impaired insulin clearance (due to increased fat and triglycerides in plasma)

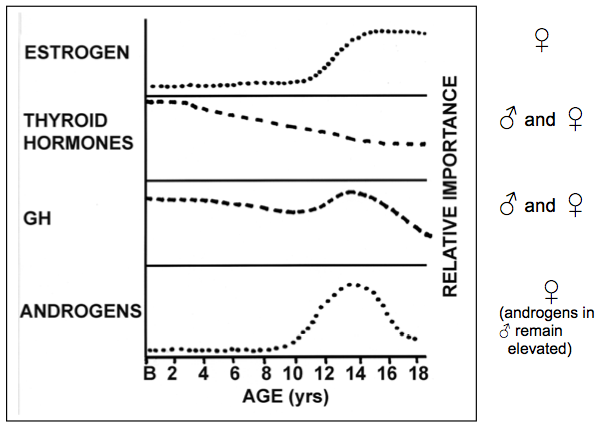
Increased insulin resistance (down-regulation of insulin receptors due to excess insulin)

* + - Cytokines
      * family of proteins made mostly in liver
      * IGF-1 is a cytokine
        + is the agent through which GH promotes growth
        + IGF-1 BP is a binding protein in blood that regulates IGF-1 availability
        + insulin decreases IGF-1 BP
  + Genetic predispositions to PCOS
    - Hyperinsulinemia
      * If you only have this issue and not the one below, then you don't have the overproduction of androgens in the adrenals.
    - Cytochrome P450c17α hydroxylase excess
      * Due to hyperactivation of the gene encoding an orphan nuclear receptor named steroidogenic factor-1 (SF-1), which is required for synthesis of the P450-assisted enzyme
      * Allows hyperproduction of androgens in ovary and adrenal
  + Diagram of PCOS Etiology
    - 
* Therapy for PCOS
  + Case specific
  + For all obese patients
    - Weight reduction yields
      * Decreased androgen
      * Decreased insulin resistance
    - Weight reduction alone can return ovulation to normal in many patients
      * (Will help decrease the insulin resistance.)
  + For non-hirsute patients not wishing pregnancy
    - Progestin (i.e., any synthetic steroid with progesterone action), yielding-monthly withdrawal menses
    - Progestagen--such as used in some oral contraceptives
  + For hirsute patients not wishing pregnancy
    - Oral contraceptives (E+P type)
      * suppress LH/FSH to decrease androgens
      * P limits E effects
    - Glucocorticoids
    - GnRH analogues
    - Antiandrogens
  + For patients desiring pregnancy
    - Standard procedures for inducing ovulation in infertility
      * Clomiphene citrate that can induce fertility

**SEXUAL ONTOGENY**

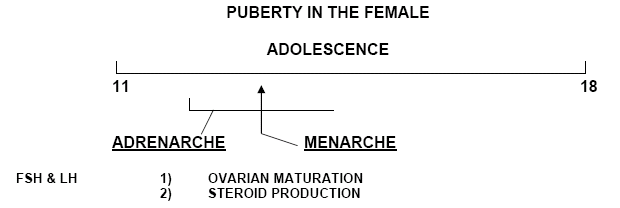
**BASIC TERMS ASSOCIATED WITH SEXUAL ONTOGENY**

* Genetic sex—XX XY or something in between
* Primary sex characteristics –gonads (ovary, testes)
* Accessory sex tissues –prostate, mammary glands
* Secondary sex characteristics—facial hair, voice characteristics, height, differences between men and women phenotype
* Puberty—a discrete point in time when reproduction becomes possible
* Adolescence—period leading up to puberty and becoming an adult
* Adrenarche—period of increased activity of the adrenal glands producing androgens in the female
* Menarche—onset of the first menses
* Menopause
  + In female, cessation of the menstrual and ovarian cycle and fertility
  + In men = andropause (more gradual than in females)
* Climacteric-- the period of time approaching menopause when physiological changes take place



* ESTROGEN
  + 1st 8 years of life little amount of sex hormones
* THYROID HORMONES
  + lots of growth and development
  + gradual decline in thyroid to reach the amount that will be present in the adult
* GH
  + Lots of growth and development
  + There is a big rise in GH during adolescence/puberty
* ANDROGENS
  + Peak in the females and then drop back down
  + In the males these remain elevated

**PUBERTAL CHANGES IN THE FEMALE**

* Puberty is that period in which reproduction becomes possible
  + term sometimes inaccurately used to describe such PREpubertal events as
    - breast development
    - growth of pubic and axillary hair
    - adolescent behavior patterns
* Menarche
  + Occurrence of initial/first menses
    - Reflecting the fact that there's been sex steroid stimulation of the endometrium
  + First several cycles usually anovulatory (5-6 cycles without ovulation)
    - i.e ,several E-withdrawal menses before first ovulation
      * They fall back down. When the estrogen is withdrawn you get the endometrial sloughing so you get the menses.
      * No progesterone secretion either and so they won't usually be as heavy of periods
  + Puberty (i.e., onset of fertility) with cyclic FSH/LH and ovulation frequently not attained until >1 year post menarche
    - Usually 6-12 months from menarche to first ovulation
      * Closer to the 6th month time usually
* Adrenarche
  + Increased adrenal androgen production associated with approach of puberty
  + Responsible for pubic and axillary hair growth
    - Note: Female pattern of distribution of this hair is due to **estrogen**
    - Growth of the hair is due to androgens but not the DISTRIBUTION
* Breast changes are first signs of approaching puberty
  + Commonly begin at 10-11
    - Might be as low as age 9
  + Usually precede appearance of pubic hair
  + Once initiated maturation of pubic hair progresses more rapidly than the breasts due
  + Breast growth continues until age 18--25
    - Most women at 18 have full breast growth.
    - Each time there is a menstrual cycle there is more estrogen present so if they have a higher receptor competency for estrogen in the breast tissue they can grow a bit more with each cycle.
* Completion of maturation requires
  + approximately 4 years for breasts
    - About the age of 15 the breast tissue is well developed but it will continue growing.
      * The mammary glands are still very undeveloped at this stage but the tissue mass of the glands and the fat in the breast will do the most growth during this period.
  + 3 years for pubic hair
* Menstrual cycles commonly begin between ages 12 and 14
* Average puberty onset age is USA has decreased 2 years since 1890
  + Principally due to improved population nutritional status
  + Also affected by enviroestrogens (women pee out their birth control), other toxins and increased stress of modern life (↑ in ADD and Autism, development of internet, etc.)
* PICTURE
  + Adrenarche—12-13
  + Menarche—12-14
  + The rise in FSH and LH is due to a change in the anterior pituitary. Stimulates the maturation of the ovaries and steroid production of the ovaries. There are alterations in the anterior pituitary cells in the sensitivity to GnRH. They become more sensitive initially and later, they become less sensitive.
* **ESTROGEN** 
  + Growth of reproductive tract
  + Growth of breasts
  + Bone growth and phenotype (body size & shape)
    - fairly anabolic hormone
    - Body size and shape along w/some help from androgens
  + **Distribution** (not growth-- that's androgens) of pubic and axillary hair
  + Influence expression of personality and sexuality
    - Basic effects of personality: cortex, limbic system, hypothalamus
* **ANDROGENS-** **primarily testosterone**
  + Growth of pubic and axillary hair
  + Primary libido hormone (stimulate sex drive)
  + Can have modifying effects on growth & phenotype
    - Due to estrogens
    - Height, girth, pear vs t shape. Determined by relative relationships between amount of estrogens and androgens present and the receptor competency
  + Influence expression of personality and sexuality

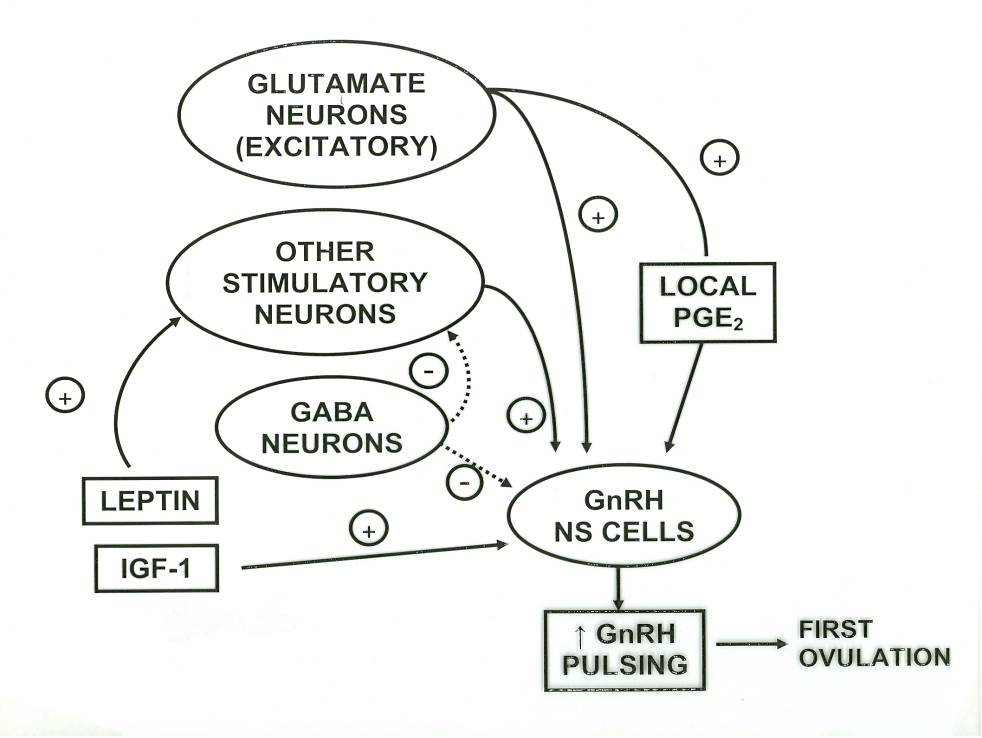
**CRITICAL BODY MASS AND SEXUAL DEVELOPMENT**

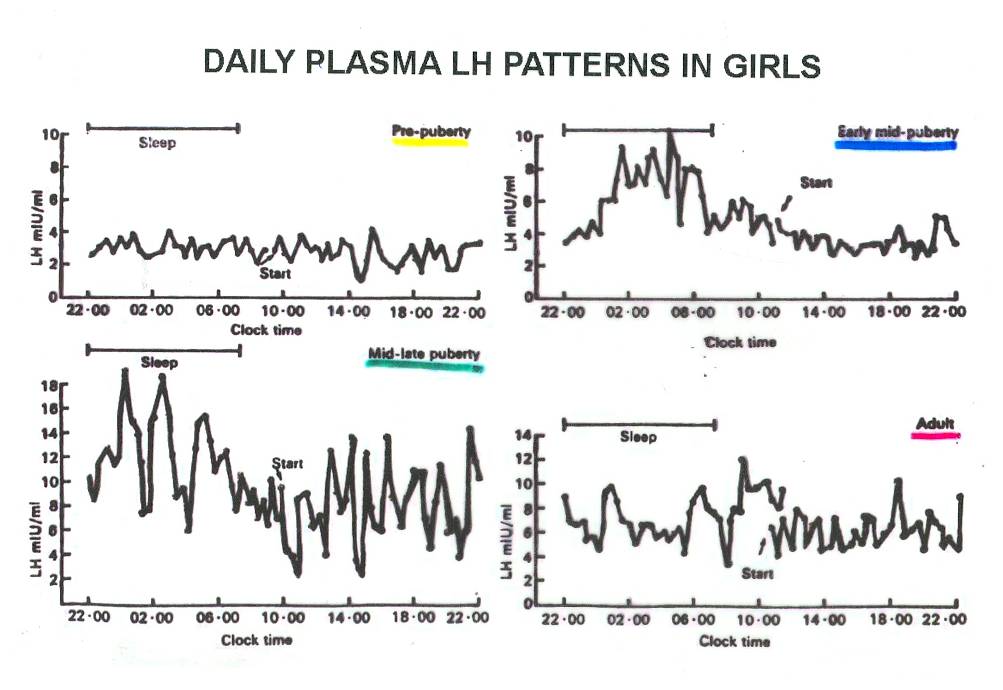
* Body mass and fat content thresholds for sexual development -- Are they determinants of puberty? Probably not but they're related.
  + Minimum weight for onset of growth spurt = 30 Kg.
  + Minimum weight for menarche = 47 Kg.
  + Fat: Lean ratio increases during growth spurt (before they actually reach puberty)
  + Minimum fat for menarche = 11 Kg. (of the 47 Kg)
    - 11 Kg. = 99,000 available calories
      * 80,000 calories needed for one complete pregnancy
      * Guarantees that there is enough calories for a pregnancy to be possible
    - But fat: lean ratio not proven to regulate puberty onset
      * Leptin is very important in the puberty
* Metabolic signals, can increase GnRH and can accelerate puberty
  + **IGF-1 and Leptin** (possibly also kisspeptin)
    - IGF-1 is stimulated by GH
    - Permissive effects
  + Requires normalcy of other hormonal changes in puberty
* Proper caloric intake and hormonal status necessary for normal puberty (and menses)
  + Energy deficits yield decrease in thyroid hormone (T3/T4), LH and GnRH pulsing
    - Can precipitate periodic to chronic amenorrhea.
    - Caloric Deficiency/Amenorrhea
      * High correlation exists
      * General examples
        + Chronic excessive exercise
        + Bulemia
        + Anorexia
    - Specific example:
      * Study of > 100 women showed 45% anovulation associated with running 15 miles per week vs. 10% anovulation in non-exercising controls)
        + The amount of women not exercising only 10% had amenorrhea

**PUBERTAL CHANGES IN THE MALE**

* Time course of pubertal changes in the male are similar to the female, but events differ.
* FSH and LH levels increase gradually (no cycles) between the age of 8 and 10.
  + Due to increased sensitivity in the anterior pituitary
* Enlargement of the testis occurs at age 10-11
  + First and major visible change approaching puberty
* Testosterone levels increase steadily and gradually (no cycles) from age 11-13, and adolescent changes in boys are due primarily to increasing androgen.
  + Greatest increase from 13-16
    - A growth spurt driven by testosterone and androgens from the adrenal as well as GH
* Pubic hair growth begins about age 12
  + Body growth spurt begins before 13
  + May last >3 years.
    - rapid muscle mass and height
    - attitude changes
    - facial hair
    - deepening of the voice
* During growth spurt
  + Penile growth
    - gets the adult size penis at age 16
  + Secondary sex characteristics
    - Facial hair
    - Deeper voice
    - Male phenotype
* Onset of spermatogenesis (i.e., fertility-- puberty for the male) occurs around age 13

**NEUROENDOCRINE CONTROL OF PUBERTY**

* Involves limbic system function (the ancient changes of the brain involved with the amygdala)
* From age of 4 to 11 years, both sexes show
  + Minimal gonadotropin secretion (small rise age 8-10) but not enough for the full development
    - Partly because of increased sensitivity in the pituitary to GnRH
  + Suppression of pulsatile secretion of GnRH From age 4-11
    - it is suppressed by the amygdala’s stria terminalis pathway
* Gonadotropin secretion increases peripubertally
  + Due to metabolic and neurochemical changes governing GnRH-producing cells
    - The amygdala suppresses GnRH-producing cells via stria terminalis
    - During pubertal period the inhibition of GnRH diminishes so less suppression from the amygdala
    - Activation of adult-type pulsatile GnRH release requires stimulation of GnRH neurons by both hormones and neurotransmitters
      * GnRH also begins to pulse
* In addition, increasing gonadal and adrenal sex steroids (small increases but effective positive/feed forward system)
  + Raise sensitivity of the pituitary cells producing LH and FSH.
    - Estrogen increases the receptors for LH
* The above lead to increased FSH and LH release, which result in further increases in gonadal steroids.
* Increased FSH, LH and gonadal steroids stimulate and guide gametogenesis.



* PREpuberty (girls before 10) show low and small pulses, very little surges
* EARLY-MID Puberty—At night there is increased LH and pulsing but during the day it was low
* MID-LATE Puberty—large pulses of LH tells us that the GnRH is pulsing considerably. Also starts pulsing during the day as well as night
* ADULT—peaks of LH but not giant ones similar to youth

**SUMMARY OF THE CONTROL OF PUBERTY**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Developmental Status** | **Hypothalamus** | **Pituitary Sensitivity to GnRH\*** | **Hormonal State** | | |
| **GnRH** | **FSH & LH** | **Sex Steroids** |
| **PREPUBERTAL (CHILD)** | Amygdala inhibits GnRH neurons via stria terminalis | Low | No pulsing | Low level | Low level |
| **PERIPUBERTAL** | Less inhibition by amygdala | Increasing | Pulsing begins | Increasing | Increasing |
| **PUBERTAL** | 1) Minimal GABA inhibition  2) ↑ Glutamate-type neurotransmission  3) ↑ Local PGE2-- acting directly on the GnRH cells in the hypothalamus  4) ↑ IGF-1 and Leptin-- works on association neurons that are impinging on the GnRH cells in the hypothalamus-- max sensitivity in the anterior pituitary | Maximal | Adult-type pulsing | Adult level | Adult level |

* \* = As puberty approaches, gonadotrophs become sensitized to the GnRH by sex steroids (probably via  receptors for GnRH).

**SEXUAL AGING IN THE FEMALE – MENOPAUSE**

* Menopause is the cessation of the menstrual cycle.
  + Normally occurs between 45-50 years of age
  + Due to senescence (aging) of the cells in the ovary (can no longer grow follicles)—they become unresponsive to the hormones
  + Hypothalamic-pituitary system (GnRH, FSH, LH) is normal
  + Usually (not always) menopause preceded by (it can be for several years or much shorter and for some women it just shuts down)
    - A number of shorter cycles (shorter follicular phase)
      * Meaning the follicular phase is shorter so follicles aren't growing or growing less
    - With longer intervals between menses
      * You don't have to have ovulation to have menses. So you could have stopped ovulating but can still have the menses
  + This pre-menopause time of physiological and psychic changes is called climacteric
* Reproductive system conditions of menopause include:
  + No ovarian follicles -- they've all become atretic
    - Takes a while for this to occur where there are no more follicles. The follicles that are left have aged to the point where they don't respond well to the GnRH pulsing—partly due to decrease in the receptor competency and also in the amount of INHIBIN- The small antral follicles in the ovary produce inhibin and there is less inhibin and the loss of inhibin will result in decreased FSH. Inhibin inhibits the production of FSH (doesn't affect LH)—important in the male
  + No ovulation
  + No menses
  + Elevated FSH and LH and GnRH because there is low negative feedback from estrodial and progesterone
  + Low E and P
* Other phenomena commonly associated with menopause (primarily due to lack of estrogen) are listed below. Most women experience some of these.
* They get the opposite of the PMS - CNS tissues can be affected and they are dependent on certain levels of estrogen. Some women have mild and some women have severe emotional conditions. Critical that each women be treated as an individual because some women have very little effects from this.

|  |  |
| --- | --- |
| **CONDITION** | **COMMENT** |
| Osteoporosis | Loss of Bone Ca++ and matrix |
| Emotional Problems | Mild to Severe—b/c of lack of CNS sensitivity to estrogens |
| Skin Changes | Wrinkling and Thinning |
| Metabolic Changes | ↓ anabolism, ↓ calories burned—b/c estrogen is an anabolic hormone- can cause weight gain. But over time they'll lose weight due to less anabolism |
| Atrophy of External Genitalia | Loss of fat in the vulva and connective tissue |
| Thermoregulatory Problems | Hot flushes due to direct action of **↑ GnRH** on thermoregulation neurons (i.e., not a direct E-loss)-- the loss of estrogen causes less negative feedback so the GnRH goes up and that causes the hot flashes |

**HORMONE REPLACEMENT THERAPY (HRT) IN MENOPAUSE--** usually the hormone is estrogen

* HISTORY
  + In 1940 the average lifespan for women worldwide was < 50 yrs, i.e., many did not outlive climacteric. In 2008 more than 700 million women were living well beyond age 50. So, the issue of E replacement for supporting quality of life is of major importance.
    - Most women were dying before they were reaching menopause
* ESTROGEN REPLACEMENT CONSIDERATIONS
  + Low-dose synthetic E (less than in OC’s)
  + PROS
    - Prevents the common degenerative changes in menopause
    - Lower incidence of hip fractures and colon cancer
    - ↓ in risk of Alzheimer’s
    - improved memory and mental function in patients that get Alzheimer’s
  + CONS (individual- and age-specific)
    - ≈ 26% Increased risk of breast and endometrial cancer
      * note: ≈ 23% decrease in breast cancer risk in full hysterectomized women
      * 25% of women over 50 get a hysterectomy
    - ≈100% Increased risk of heart disease, stroke and thromboembolism
      * The use of hormone replacement therapy involves a lower dose of estrogen than in oral contraceptives (about half). So if a women had already had issues with contraceptives than she needs to be wary about HRT
    - Side effects include uterine/vaginal bleeding, bloating, and breast tenderness
      * It's estrogen only. Not really progesterone. Some women use progesterone to limit the side effects of estrogen. If you put too much progesterone in there you'll just block the effects of estrogen so you don't want that.
      * “Women’s Health Initiative” Project
        + 1991-2003, including HRT trial (16,000) menopause women
        + Showed increased health risks from RT, mostly for women over 65 (minimal for 50-65)

Health risks from ages 50-65

* + - * + Nonetheless this scare decreased HRT use >50%

After this 50% decrease in women who used HRT. But was it worth it? Especially the quality of their lives.

* + Additional considerations
    - HRT currently benefits millions of women (many in the safer 45-65 age range)
    - Risk expression issue
      * Example:
        + Change from 1 woman per 1000 cases to
        + 2 women per 1000 cases is 100% ↑
* The Bottom Line - HRT can be valuable quality-of-life tool
  + Especially from menopause to age 65
  + Each patient must be treated individually
  + Proper screening and long-term monitoring assure optimal outcome.
* Approach to HRT treatment requires patient-specific assessment
  + Severity of estrogen-loss symptoms
  + OC side-effects history
  + Family history of
    - Cardiovascular disease
    - Reproductive cancers
  + Patient-age context for risks
  + If E-therapy chosen:
    - Start at lowest dose
    - Tritrate to effectiveness
    - Monitor for problems
  + If cannot use E-therapy
    - Use non-estrogenic and symptom-specific alternative therapy
      * EXAMPLE: Evista
        + Selective E2 Receptor Modulator (SERM)
        + It can Bone preservation and ↓ cholesterol
      * EXAMPLES: Alendronate, Boniva, Reclast
        + Osteoclast inhibitor (major) - osteoblast stimulator (some)

**SEXUAL AGING IN THE MALE**

* Reproductive senescence in male is gradual, usually beginning after age 60 (commonly referred to as **ANDROPAUSE**).
* Many males remain sexually active through old age, into there 80's and 90's.—Can even remain fertile!
* Men over 70 exhibit (The first 3 things means less effects of androgens)
  + ↓ plasma T
  + ↑ TeBG
  + ↑ aromatization (estrogen formation)
  + ↑ FSH and LH
  + ↓ sperm count (↓ 30% or more)
* Androgen replacement therapy can be useful for retarding degeneration that occur with lower androgens and improving quality of life.
  + A number of physicians now pursue andropause medicine as a career focus
  + But the risk factors aren't as bad
* Amount of androgen used for replacement is small, so not dangerous like anabolic steroids.

**SEX HORMONE REPLACEMENT IN MALE AGING**

* Androgen is the major hormone type used for replacement
  + Testosterone (T)
  + Dehydroepiandrosterone (DHEA, in part acts to ↑ IGF-1)
    - much weaker androgen with a lot of the same benefits as testosterone
* Effects in replacement use
  + Both maintain skeletal muscle
    - 25% less muscle mass at age 70 than 40
  + Both increase energy
  + Both increase libido (Viagra-type agent often used in addition).
  + DHEA milder and safer than T
    - 1) T ↑ prostate tumor
    - 2) T ↓ sperm count
    - 3) T ↑ aggression
* As with E replacement in women, androgen replacement in men requires proper screening and long- term patient monitoring to assure optimal outcome.

**DEHYDROEPIANDROSTERONE (DHEA) AND AGING**

* Not as aggressive of a hormone
* Plasma DHEA decreases beginning in the 50’s (in both sexes)
* DHEA effects
  + ↑ lean body mass
  + ↑ joint flexibility
  + ↑ insulin and IGF-1
    - increases anabolic behaviors
  + ↑ facial hair (problem for use by women) and acne
  + Antilipogenic
* DHEA Pros and Cons
  + Pros
    - Inexpensive ($10/mo)
    - Less bioagressive and fewer side effects than T or anabolics
  + Cons
    - Very few controlled studies
    - Zero info on long-term effects
    - No quality control in manufacture
      * not a government controlled substance

**CORTISOL RECEPTORS AND AGE**

* There is less negative feedback on cortisol in old age, so cortisol levels gradually increase.
  + Down regulation of CNS cortisol receptors
  + ↑ Neuronal death
* Increased cortisol in old age leads to:
  + Memory loss due to cortisol receptor down regulation and neuron death in hippocampus (important memory site)
  + Impaired stress response and slow recovery from stressors due to deranged cortisol feedback and cortisol receptor down regulation
    - Since cortisol prevents overreaction to stress
      * Response to stressors is blunted in old age
      * Recovery from stress is slower in old age
  + Faster tumor growth in old age due to direct immunosuppressive effect of cortisol.

**SEXUAL BEHAVIOR & SEXUALITY**

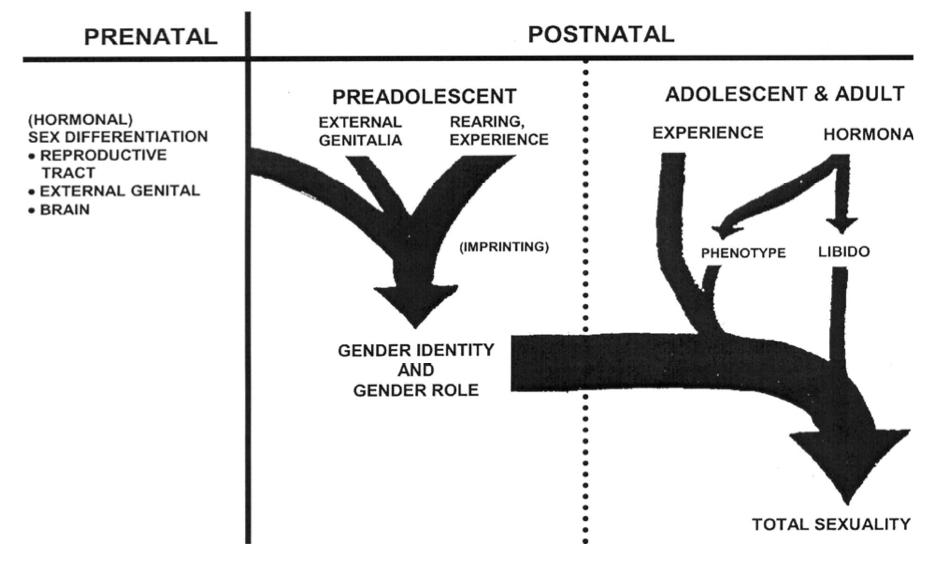
**SEX, LOVE AND SPECIES SURVIVAL**

* Species survival requires
  + Parents reproduction
  + Rearing of offspring
  + Offspring reproduction
  + INSURED by
    - Sex drive and attraction
    - Social roles and values
    - LOVE
* Species survival roles
  + **Male**
    - Relatively non-selective mating o goal is to spread genes
  + **Female**
    - Generally selective mating
    - Goal is reliable partner to assure success raising offspring true in primates
      * not so much mountain lions, etc.

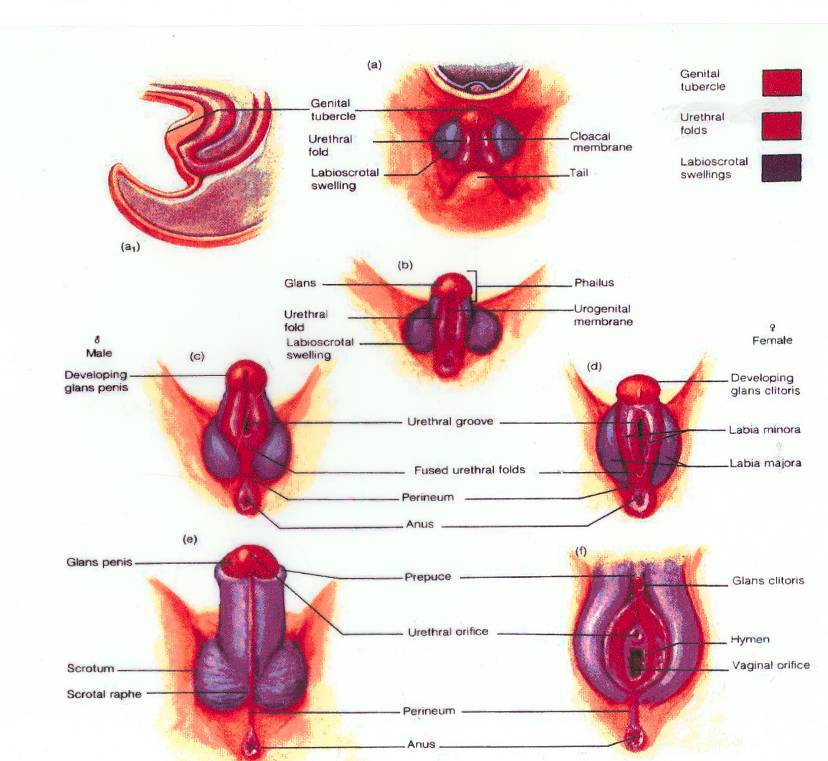
**SEXUALITY AND PSYCHOPHYSIOLOGY**

* Interactive limbic pathways link cognition with
  + Sex drive, sexual awareness, mood-emotion, and memory.
    - Olfactory memory is extremely important to sexual behavior adolescents have a sexual thought every 12 seconds FYI
* **Therefore:**
  + Sex can be used to sell clothes, cars, beer, etc.
    - Reported 4 years ago that pornography makes more money than google, yahoo, etc.
  + Sexual attraction can produce out-of-character behavior.
  + Sex is a hard-wired component of our individual identity
    - How we project ourselves (gender role) and perceive ourselves (gender identity).
  + Sex is an integral part of our social patterns (courtship, marriage).

**FACTORS DETERMINING SEXUALITY**

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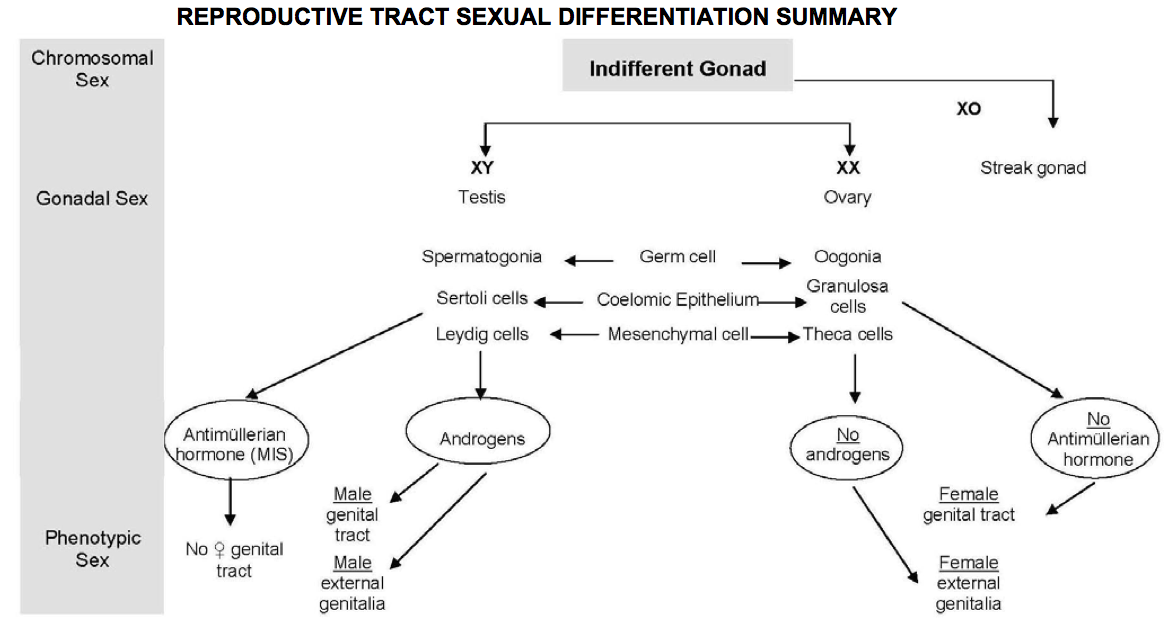
**SEXUAL DIFFERENTIATION**

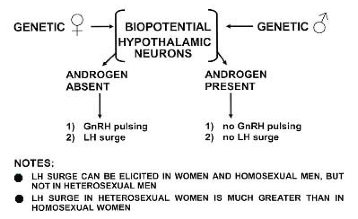
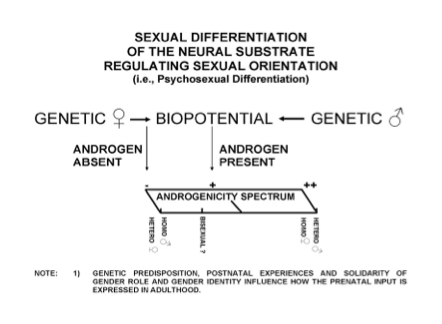
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**4 Primary Sites**

* GONADS, EXTERNAL GENITALIA, INTERNAL DUCTS, & BRAIN
* **Gonads (weeks 6-9)**:
  + Common primordia under genetic control
    - XX or XY or something in between
  + Male (testis) begins by 6 weeks
  + Sex determining region on Y chromosome (SRY gene) causes testis to develop
    - SRY activates testis-promoting transcription factor (Sox9)
    - Sox9 initiates development of important testis cell type (Sertoli cells—critical for male reproduction)
  + In absence of Y chromosome ovaries develop (weeks 7-9)
    - Requires epithelial mitogen (R-spondin-1) that may turn off Sox9 protein that is necessary for maleness
      * The R-spondin 1 is a testis inhibitor. Acts via cell adhesion proteins that are necessary for the normal formation of the ovary.
* **Internal genital ducts (weeks 8-12)**:
  + Week 7: choice time
  + Week 8: if it's an ovary that starts happening
  + Separate sets of primordia which transiently coexist in embryos of both sexes
    - There are 2 separate sets of primordia.
  + Maleness requires the positive influences of two components
    - Testosterone
      * grows Wolffian (male) ducts (will become vas deferens, epididymis, etc)
    - Müllerian Inhibiting Substance (MIS)
      * glycoprotein from fetal testis
      * prevents Mullerian (female) ducts
  + Absence of T and MIS yields Müllerian (female) ducts
    - if you don't have T or MIS = female
    - If you have T but not MIS= you'll have both female and male duct system internally
    - if you don't have T but you do have MIS = you won't have either duct system
* **External genitalia (weeks 8-12 of gestation)**—develop at the same time as the internal genital ducts
  + Common primordia undergo continuous process (not “either/or”)
    - There can be in between stages of development. So you can end up with an enlarged clitoris or a small open penis on the ventral side basically things can stop at this stage
  + Maleness requires the positive effect of dihydrotestosterone (DHT) alone
    - DHT is a product of testosterone due to 5-α reductase enzyme.
    - If the enzyme is there then this is formed and maleness external genitalia can form
  + When androgen effect is intermediate, newborn shows partial virilization
  + This differentiation is virtually **complete by the 16th week**
  + If testosterone not present in first 12 weeks, masculinization never complete.
  + Conversely, genetic females with excess androgen (such as if they have congenital adrenal hyperplasia) may have females that have complete phallic urethra and prostatic tissue

**REPRODUCTIVE TRACT SEXUAL DIFFERENTIATION SUMMARY**



* In the embryonic ovary you don't have androgens! Remember the thecal cells in the adult when you have a menstrual cycle going on make androgens that get shuttled to the granulosa cells to make estrogen but in the embryo this does not happen.
  + You do have this after menses to stimulate them to form estrogen
* Sertoli cells have the MIS which can inhibit female genital tract formation and the androgens from the testes help aid in male genital tract formation and the testosterone helps induce the external genitalia
* Remember all of these choices are made by 12 weeks of pregnancy!
* **Brain**
  + 2 foci of sexual differentiation
    - control of gonadotropin-release
    - psychosexual differentiation
  + process occurs in gestational weeks 8-12
  + Gonadotropin-release sexual differentiation (weeks 8-12)
    - Certain hypothalamic neurons of both sexes are initially bipotential, i.e., capable of becoming functionally male or female.
    - During a steroid-sensitive period of development (1st trimester in humans) androgen presence causes permanent, irreversible biochemical changes in these neurons, and the brain area containing them becomes 2x larger in the male vs. the female (where the androgens are absent)
      * The way they behave in regulating the release of GnRH is permanently set in these neurons in weeks 8-12
      * If androgen is present in normal male levels it will prevent cyclic LH activity meaning that LH won't surge 🡨 that is necessary for female menstrual cycle
      * This situation (normal in the male) results in the inability of the adult hypothalamic-pituitary system to produce the cyclic pattern of GnRH and gonadotropin release.
    - Thus, regardless of genetic sex, the presence of androgen (at levels normal for the developing male) during this prenatal critical period prevents cyclic (female) hormone pattern essential for the menstrual cycle, and leads to the pattern characteristic of the adult male.
      * Prevents cyclic LH release-capability development
    - Absence of androgen (or very low levels) during this critical period, regardless of genetic sex, allows adult capacity to show the cyclic pattern of GnRH and gonadotropin release essential for menstrual cycle.
      * Allows cyclic LH release pattern to development
      * This is the normal female condition.
      * LH surge can be elicited in the females and homosexual men suggesting that there may be some deficiency in androgens in homosexual men during this critical stage of development (still part of normal but a deficiency)
        + Also LH surge in homosexual women is less than that in heterosexual women
  + **Psychosexual Differentiation (weeks 8-12; and postnatal)**
    - A steroid sensitive period (1st trimester in humans) exists for anterior hypothalamic neurons (different from the ones that regulate GnRH) involved in the display of sexual behavior. The area containing these neurons is 2x larger in male vs. female.
      * Remember that the preoptic area of the anterior hypothalamus is NOT where GnRH is made, It's where the neurons that impinge on the GnRH producing neurons in the arcuate nucleus at the base of the hypothalamus are located
    - In non-human mammals, regardless of genetic sex…
      * In most mammals presence of androgens (regardless of genetic sex) causes  these neurons (primarily in the hypothalamus) to become permanently and irreversibly organized to favor expression of male sexual behavior in the adult.
      * Absence of androgen (regardless of genetic sex) favors expression of female sexual behavior in the adult.
        + Estrogen may be involved but issue not resolved

Realize that the androgens can be aromatized to estrogens but we're not sure what role this plays

* + - In the human, the situation is much more complex.
      * Sexual differentiation of the neural substrate is similar, but **postnatal factors**  (social values, rearing and personal life experiences) can greatly mold an individual's  sexual orientation and sexual behavior.
        + One of the reasons why homosexual people can come out later in life (you have a predisposition but other factors play a role in sexuality)
      * Thus it appears that androgen presence during sexual differentiation favors but  does not determine development of masculine sexuality and the androgen absence, during sexual differentiation favors but does not determine development of feminine sexuality.
      * The amount of androgen required for this prenatal process is unknown, but it appears that degree of favoring is somewhat proportional to the amount of androgen present during sexual differentiation and the androgen receptor concentration in the CNS
* **SUMMARY:**
  + In summary the available evidence indicates the development of homosexuality has some roots in the amount of androgen present during psychosexual differentiation.

**ADDITIONAL NOTES REGARDING PSYCHOSEXUAL DIFFERENTIATION**

* The brain area undergoing psychosexual differentiation is 2x larger in the heterosexual male compared to the female or the homosexual male.
* Adrenogenital women (they had congenital adrenal hyperplasia), despite being corrected in infancy, show increased bisexual and homosexual Fantasies (playing the ‘male/dominant partner’ role).
* Chronically elevated cortisol (stress) suppresses testosterone in male fetus during pregnancy (8-12 weeks gestation)
  + If it occurs during the 8-12 weeks of pregnancy these women may end up having XY/male fetuses but they were greatly testosterone suppressed.
    - **EXAMPLE:** The incidence of homosexuality in German males was about 3x greater among those born during W.W.II than among those born before or after.

**GENETIC BASIS OF SEXUAL ORIENTATION**

* In addition to hormonal role, there is a gene on X chromosome (q28 region) which appears to code a predisposition for homosexuality in genetic males.
  + This study was first reported in 1991. The evidence is pretty clear that there is some sort of predisposition for homosexuality in genetic males.

**SEXUAL AMBIGUITY**

* Most commonly due to:
  + Incomplete external genitalia development at birth
    - There may be problems with the internal duct system as well but this has little effect on whether or not the child is raised as a boy or a girl.
  + External genitalia complete but opposite of genetic sex
    - Example - congenital adrenal hyperplasia
      * Depending on the intensity of it
      * XX that were exposed to too much androgen looks like a boy
    - Example - androgen insensitivity syndrome (talked about the first day of class)
      * XY without enough receptors for the androgens look like a girl
    - Example - 17 α hydroxylase deficiency (rare)
* In the case of the examples above:
  + Incorrect sex assignment often not discovered until puberty (e.g., no menarche in androgen insensitive XY)
    - That's when they discover that they are XY.
    - Most of the time the person remains as a girl.
    - Deficiency of androgen receptors in XY or excess androgens in XX
  + Social and psychosexual orientation are well developed by puberty, so “apparent” sex is  retained and genetic sex ignored
    - Try to match to the gonads
* Issues of sex reassignment for an adult
  + Patient wishes vs. what is possible
  + Extensive counseling to assess patient commitment
  + Surgery and/or hormonal therapy
    - corrective surgery at a very little age unless it's something like an incomplete vagina where you have to wait until they're an adult
* Guidelines for successful sexuality development in cases of ambiguity at birth are listed below:
  + Choose the sex based on likeliest outcome, i.e., try and match to gonads, external genitalia.
  + Parent-doctor commitment to one sex, no ambiguous signals to child because can really screw up their identity
  + Early corrective surgery toward chosen sex (preferable before 6 mos., OK up to 18 mos.)
    - If you want to correct a malformed vagina you should wait until adolescence when the tissue is more adult like
  + Give sex hormones of chosen sex as puberty approaches so they can have a normal pubertal experience
  + In age-graded steps, keep child informed of the process in reasonable, simple terms
    - You should keep them informed!
* Surgical intervention:
  + Before 6 mos. for clitoroplasty (reduce the size of the clitoris) and hypospadius repair (no closure of the ventral side of the penis), but OK up to 18 mos.
  + After 30 mos., major associated psych problems can occur
    - The child already has their gender identity by this point!
  + Vaginal reconstruction best in adolescence
  + \*\*What the patient wants vs what is possible much easier to go from a male to female than a female to a male
    - extensive counseling is needed and suggested for 2 years before a choice like this is made

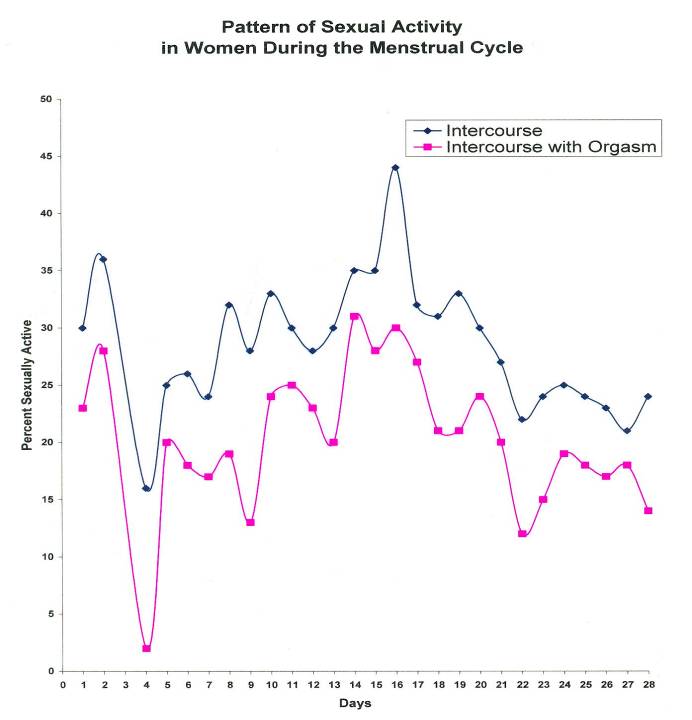
**HORMONAL CONTROL OF LIBIDO**

* Male vs. Female
  + **MALE 🡪 Androgens from testes LIBIDO**
  + **FEMALE** 🡪 **Androgens from adrenal gland (& ovary) LIBIDO**
* Hormones from ovary may alter libido across the menstrual cycle.
  + Estrogen and progesterone can influence the sex drive more or less
* E or P in large amounts (some oral contraceptives) can inhibit libido in both sexes.
  + Estrogen and progesterone in oral contraceptives (pharmacological doses) can inhibit the sex drive in males and in females
  + Estrogen more stimulatory for sex drive and progesterone more inhibitory
* Androgen increases intensity of sex drive but doesn’t change direction of interest.
  + Won't make a homosexual straight
* Androgen deprivation results in incomplete loss of libido, suggesting behavioral conditioning component of libido.

**PHEROMONES (Vomeropherins)**

* Airborne molecules which act via the olfactory system to influence drives and behaviors
  + Chemical messages from one organism to another
  + Express a physiological/behavioral state to the recipient that yields a response from the  recipient
    - Dogs scent mark and pee on hydrants, etc.
* Important communication system for many species
  + Most likely reception pathway in mammals is via vomeronasal organ in nasal septal mucosa
  + in some species it's very important and in humans it's there but not much of a role
* Involved in:
  + Social recognition
  + Territorial marking
  + Location mapping (where other animals are)
  + Sexual attraction
* Chemistry and Effects
  + Volatile steroids (they are steroids but not E2, P or T action) -- not estrogen, progesterone or testosterone
    - Present in axillary sweat
    - Subtle emotion/mood effects
    - Can advance/retard timing of ovulation
  + Short-chain aliphatic acids
    - Present in vaginal secretions
    - Example: **Copulins**
      * Agents that stimulate male libido (primate studies)
        + Studies in rhesus monkeys aromatherapies to change mood and they'd put chemicals on the fur to make the monkeys want the female monkeys and one of the scents was the “candy good and plenty” which made the male monkey go CRAZY it was essentially licorice
      * Highest production around ovulation
      * Decreased by oral contraceptives so they will have lower levels of copulins

**PATTERN OF SEXUAL ACTIVITY IN WOMEN DURING THE MENSTRUAL CYCLE**

****

* Right after menses has ceased and the estrogen levels are at their lowest and there was lower incidence of organs
* There was the greatest level of orgasm during ovulation when estrogen levels are at their highest and copulins are also at their highest

**SEXUALITY SUMMARY**

* *From a strictly physiological perspective*:
  + The hormonally-determined process of sexual differentiation of the reproductive system and  brain contributes to the development of sexuality.
  + The hormonal environment in adolescence and adulthood contributes to both development and expression of sexuality.
    - Prenatal component, chlildhood component, Adulthood and life experiences and hormones
  + Pheromones can enhance sexual attraction and expression of behavior.
* *Non-physiological factors which must be considered include*:
  + Possibility of genetic predisposition for sexual orientation.
  + Social and cultural norms and values affecting attitudes and expression of sexuality.
    - Social constructs like marriage and courtship, etc.
    - Saw that with the appearance of pubic hair (caused by androgens) starts the male sexual drive
    - Females shows the same pattern of androgen present and pubic hair but there is a delay in the onset of orgasm experience over ages
  + Species-survival drives imbedded in social and cultural patterns.
* Data suggest involvement of all of the above in the development and/or expression of human sexuality
  + Relative importance of each aspect remains unclear
  + Further investigation is needed.

**HUMAN SEXUAL RESPONSE**

**BASIC PHYSIOLOGICAL EVENTS OF SEXUAL RESPONSE**

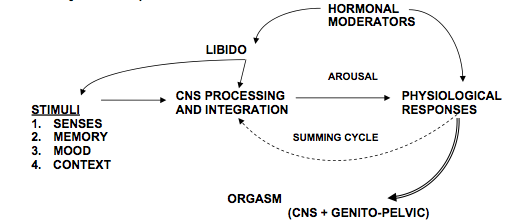
* Numerous distinct physiological events, but can be grouped into 2 basic physiological responses:
  + Vasocongestion
  + Myotonia— increased muscle tone
  + Rapid release of A. and B. due to orgasm
* Sexual response pattern can be described in 4 stages:
  + **Excitement** - Psychological arousal, initial pelvic vasocongestion in female, erection in male
  + **Plateau** - Continuation and intensification of excitement stage
  + **Orgasm** - Complex integrated CNS and pelvic events, consisting of repeated, rhythmic, contractions of perineal muscles and sensory perception of these contractions
    - ejaculation of semen in male
    - in female little or no fluid but same contractions as male
  + **Resolution** - Return to pre-excitement state (several minutes, but much longer if no orgasm)
* Physiology of erection: \*\* POINT AND SHOOT
  + Flaccid state - penis under sympathetic tone
  + Filling - parasympathetic stimulation, less arteriolar tone
  + Tumescence - nitric oxide induced vasodilation relaxes corpora cavernosa  (agents like Viagra block nitric oxide breakdown)
  + Full erection - engorgement of corpora cavernosa
  + Rigid state - engorged cavernosa obstruct venous outflow
  + Note that similar but less obvious events occur in labia and clitoris in the female

**MALE - FEMALE COMPARISONS IN SEXUAL RESPONSE**

* Human sexual response is true psychophysiological experience in both sexes
  + Variation among individuals large
  + Psychological contributions subject to large variation (i.e., what is erotic?)
    - Influenced by senses, memory, mood, context
  + Physiological events show little variation
* Excitement, plateau and resolution stages show little sex difference between male and female
  + Homologous structures respond similarly
  + Female response patterns may be more varied
    - Women might not be satisfied and the male may orgasm before the female can reach that and this may elicit frustration, etc
  + Female responses may commonly be more gradual
* Orgasm stage
  + Subjective perception (quality)
    - No consistent sex differences in written descriptions of orgasm by >2000 people
      * Kinsey institute in Indiana: sexual behavior in the human male. They examine human sexuality and behavior. Why do we behave the way we do when it comes to sex? Why are some males okay with condoms and why are some not?
  + Frequency of orgasm
    - Refractory period more common in males
      * Fluid refill of posterior bulb of urethra causes reflex contraction
      * Required for subsequent ejaculation
      * Refractory time is individual-specific
    - Multiple orgasms more common in females
    - Orgasm/intercourse ratio greater in males
* Basis for more varied and gradual sexual response in women compared to men
  + More social consequences for women
    - Antipromiscuity pressure
    - Anxiety about possible pregnancy
  + More sensitivity to surroundings in women
  + More erotic zones (less pelvic focus) in women
  + Women less orgasm oriented (YA RIGHT)
* Male-female response differences as source of relationship problems
  + Male finishes before female orgasm
  + Often an unaddressed subject
    - Frustration
    - Eventual resentment
    - Less frequent sex
* Stimuli for sexual arousal very individual-specific
  + Senses
    - Pheromones, scents
    - Visual (more important for male than for females- probably why pornography is more popular with males touch and sound)
  + Memory of previous experience
  + Mood
    - Ambience –environment
    - Feelings of closeness and attachment (more important for female—may be because females think about the option that they may have to raise a child with this person)
    - Sexual context (privacy, novelty, making up) -- energy being devoted to the act
  + Overall mix determines intensity of experience

**OVERVIEW OF HUMAN SEXUAL RESPONSE**

* Diagram of Pathways



\* hormones must be present for libido

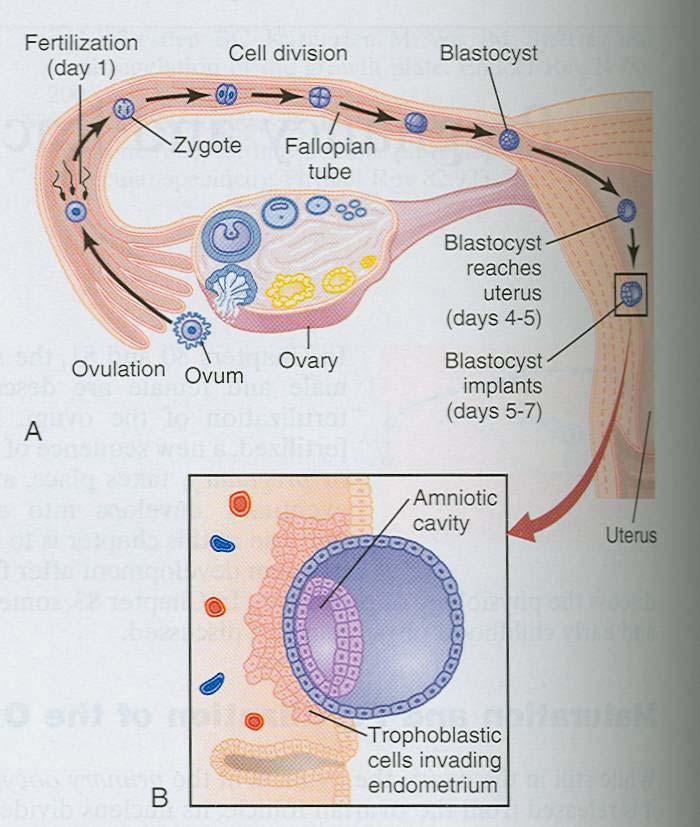
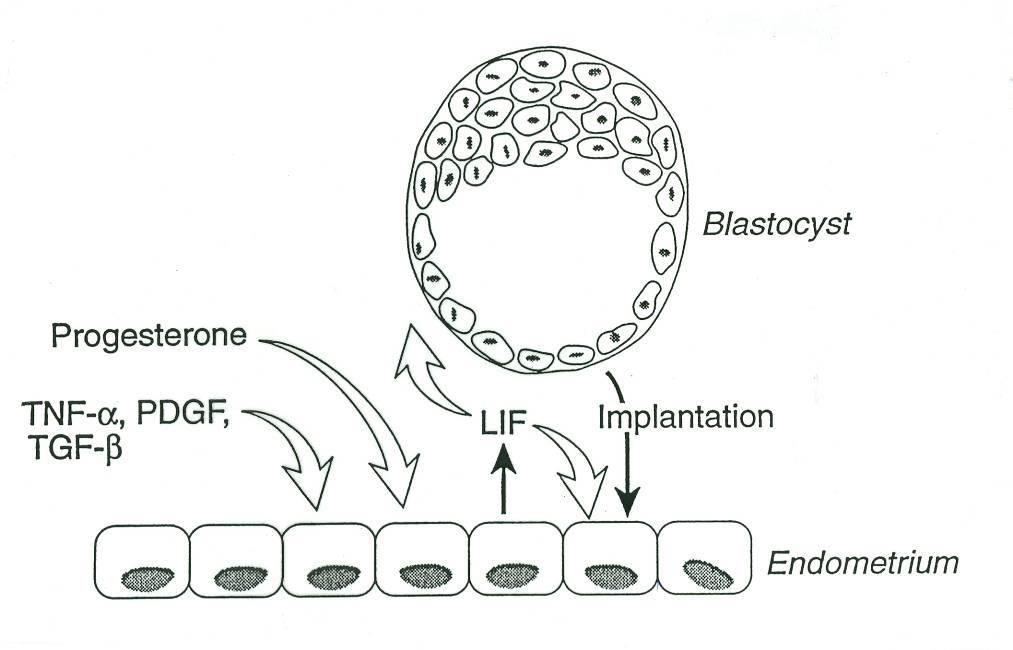
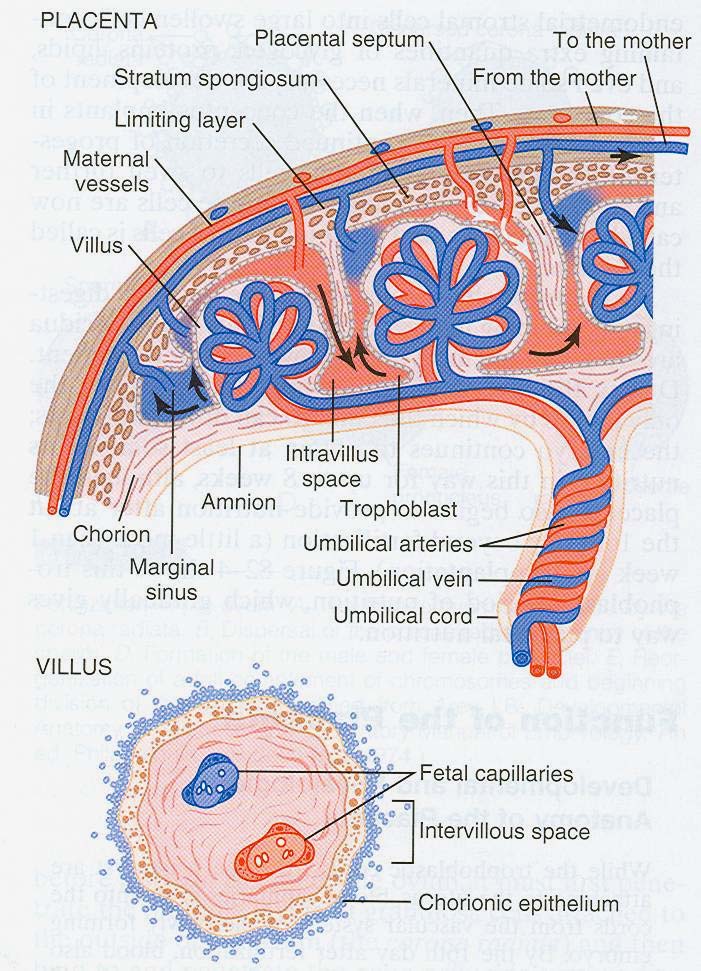
* Foci of Sexual Response
  + CNS and genito-pelvic
    - Sexual response cycle operates via integration of CNS and genito-pelvic events in a repetitive, summating (intensifying) positive feedback loop that leads to orgasm
    - When orgasmic threshold is reached in CNS, there is massive motor nerve output (via lumbar spinothalamic tract, LST) with focus in genito-pelvic (perineal) region
      * This then generates the muscle contractions in the perineal region
    - Orgasm is
      * Repeated, rhythmic contractions of perineal musculature in response to motor nerve  activity described above
      * CNS cortico-sensory experience of this
* Testosterone optimizes sensitivity of:
  + CNS substrate regulating libido
  + CNS components of the summing cycle leading to orgasm
  + Peripheral tissues involved in the sacral reflex
* CNS and peripheral events, while normally integrated, are not mutually dependent, since manual stimulation of the genitalia can produce erection, emission, and ejaculation in males and comparable events in females after complete spinal section
  + There are actually programs for those with spinal sections where they can have other zones of the body that they are taught to be sexual zones and then they can stimulate the penis/vagina manually and still get the experience.
    - They can have the sensation of the orgasm some other place in the body

**SEXUAL DYSFUNCTION**

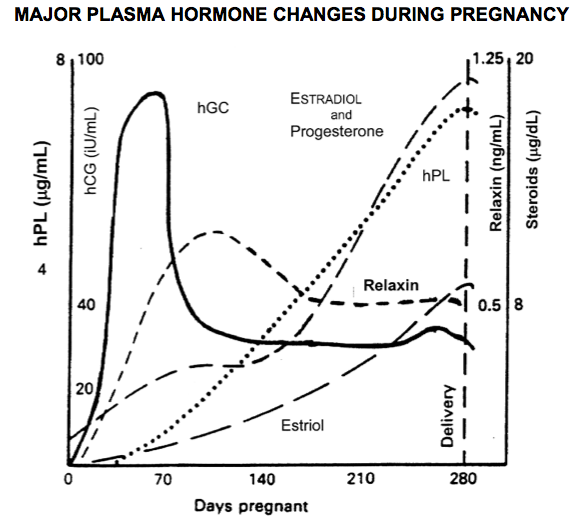
* Disorder of sexual function
  + Physical-organic (10-15%) basis
  + Psychological basis (85-90%)—persons experience in life are very important in how they feel sexually
* Feeling of sexual well-being extremely important each person's life, thus every physician should know
  + Most common sexual dysfunctions
  + How to approach treatment
* Up to 50% of patients have some sexual matter that they would like to discuss with their doctor,  but <10% actually do so
  + Physician discomfort with the subject is a significant contributor to this difference

**PREGNANCY AND LACTATION**

**THE ONSET OF PREGNANCY (POST FERTILIZATION)**

* (Fertilization is discussed in male reproduction session)
* **Germ Cell Path**
  + 
* The Conceptus (zygote to fetus)
  + After fertilization, the second polar body is formed and the new mature ovum becomes a zygote.
  + During 3 days within the fallopian tube, the zygote repeatedly cleaves to produce a 58-cell **morula**.
  + Further division yields 107-cell **blastocyst** ready for implantation
  + In the human, from two-cell stage through eight weeks of development is termed  “embryo.”
  + From eight weeks to birth, the conceptus is called a “fetus.”
* Early Pregnancy
  + 70% of fertilized eggs do not survive, most failures occur within 14 days
  + Implantation requires adhesion, penetration, and invasion.
    - Penetration—Blastocyst becomes firmly embedded in the wall of the uterus.
  + Implantation of a blastocyst is an unusual event b/c its foreign tissue implanting into the mother
    - Requires inhibition of usual immuno-rejection that follows grafting of foreign tissue (blastocyst)
    - Inhibition is by **leukemia inhibitory factor (LIF),** a cytokine produced in endometrium in response to
      * Progesterone
      * TNFα
      * TGFβ
      * growth factors (like PDGF)
      * CRH
      * hCG
  + Decidua is endometrium that interacts with trophoblast to become maternal portion of placenta.
    - Deficiency of natural killer cells and dendritic cells in decidua can lead to failed implantation/failed decidua.
* **Placenta**
  + The placenta has several critical roles:
    - Deliver nutrients to fetus (from mother)
    - Remove metabolites from fetus (to mother)
    - Produce hormones that manage pregnancy (affect both fetus and mother)
    - Limits pathogen and chemical transfer between mother and fetus
* Placentation
  + Contact between blastocyst and endometrium causes proliferation of the trophoblast
    - The trophoblastic layer were the cells that penetrated into the endometrium.
  + Trophoblast enzymes allow blastocyst to bury itself within the endometrium.
  + Nutrient-rich endometrial cells provide nutrition for several weeks, with placenta gradually taking over this role.
  + Placenta is an interlocking of maternal and fetal tissue.
  + Hemochorial type in human (fetal portion directly bathed by maternal blood)
  + Mature placenta

**MAJOR PLASMA HORMONE CHANGES DURING PREGNANCY**



* hCG levels go up pretty quickly with the onset of pregnancy and then declines
* Relaxin (dashed line) goes up in the first trimester of pregnancy probably do hCG stimulation but it actually doesn't play much role in that part of pregnancy its major effects are at the end of pregnancy
* Rise in estradiol and progesterone
* Rise in human placental lactogen
* Rise in estriol, good because it is a hormone that can serve as an indicator for fetal wellbeing

**IMPORTANT ASPECTS OF ENDOCRINE FUNCTION DURING PREGNANCY**

* If implantation occurs, developing chorion produces hCG (human chorionic gonadotropin).
* hCG maintains function corpus luteum (CL) function at the beginning of pregnancy b/c the CL is important in producing steroid hormones before the placenta takes over
  + hCG test kits can detect pregnancy 3-5 days post implantation (7-9 days post fertilization).
* Active CL continues to increase progesterone production at the early stages of pregnancy (progesterone is important to prevent contractions of the uterus) until placenta takes over.
* Between weeks 6-9 post-fertilization: the placenta is complete and, using maternal cholesterol as precursor,  becomes the major source of progesterone and other steroids, and hCG production falls off and the CL is not necessary anymore.
* By 2 months of pregnancy: human placental lactogen (hPL) levels are rising. hPL is a growth hormone-like protein of pregnancy.
  + Its not as potent as GH itself but there is a lot more hPL during pregnancy than GH
* Placental production of hPL, P and Estrogens (Estradiol and Estriol) increase throughout pregnancy.
  + Ratios of P to E need to favor P as the dominant hormone to ensure that there wont be uterine contractions during pregnancy

**HORMONE PRODUCTION BY PLACENTA**

* **MAJOR** 
  + Progesterone
  + Estradiol
  + Estriol
  + Mineralocorticoids
  + Glucocorticoids
  + Placenta lactogen
  + Chorionic gonadotrophin
  + Prolactin
  + Relaxin
  + Prostaglandins
* **MINOR**
  + ACTH
  + β-Endorphin
  + GnRH
  + TSH
  + CRH
  + GHRH
  + Somatostatin
  + IGF-1
  + Other GFs
    - IGF-1BP
  + Immunocytokines
  + Inhibin
  + Activin
* The roles of the major pregnancy hormones include:
  + hCG (38,000 MW glycoprotein, similar to LH)—at the beginning of pregnancy
    - Keeps ovarian corpus luteum (CL) active until placenta takes over
    - Aids in endometrial immunotolerance and placentation
      * Avoids graft rejection (fetus as a graft)
    - Stimulates relaxin production
  + Progesterone
    - Insures no more ovulations
    - Prepares endometrium for implantation
    - **Inhibits myometrium contraction**, preventing expulsion of embryo/fetus
    - Serves as substrate for fetal adrenal steroid production
    - Blocks uterine cellular immune response to foreign antigens, i.e., prevents fetoplacental  “graft” rejection (**partly via ↑ LIF**)
      * PROGESTERONE IS PROBABLY THE MOST IMPORTANT ONE!!
  + hPL (human placental lactogen)
    - Has both GH and PRL (prolactin) properties; structurally and immunologically most similar to GH;  MW = 22,500
    - Weak GH activity (2-5%), but plasma hPL levels are 100 X GH levels, so is an important pregnancy GH
    - **Anti-insulin action**, causes poor glucose tolerance in pregnancy (some pre-clinical diabetics become overt diabetics)
    - Inhibits activity of mammary milk-producing cells—lactation doesn't come on strong until after pregnancy
  + Estrogens
    - Plasma levels increase throughout pregnancy (but P still predominates during pregnancy)
    - **Estradiol 17β** 
      * Supports uterine structure and function and mammary gland development (along with progesterone🡨both actually work on different parts on mammary gland production)
        + *For example: Upregulates receptors for growth factors and progesterone*

Weird that it upregulates receptors for a hormone that is basically antagonistic to it

* + - * Contributes to fetal organ growth and maturation
      * 50% is maternal, so cannot use as fetal well-being indicator
      * Increases plasma binding proteins
        + Significant enough to change the amount of available hormone change; ex: it upregulates cortisol binding protein so it actually ↓ free cortisol in the blood (plays a role in parturition and onset of lactation)
    - **Estriol (has 16 hydroxl group added to estradiol)**
      * A very weak estrogen, but level in urine can be clinical indicator of fetal well-  being, because fetus and placenta must work together to make estriol.
      * In the Estriol pathway
        + Placenta lacks an enzyme that makes DHEA in the estriol pathway
        + Fetus lacks an enzyme post-DHEA in the estriol pathway
        + Problem is circumvented by fetus making DHEA in the form of 16αOH DHEA sulfate and this is passed it to the placenta, which converts it to estriol
      * **Steroid sulfatase deficiency syndrome** (due to DHEA sulfate excess)
        + X-linked recessive disorder
        + Associated with low estriol and excess DHEA sulfate

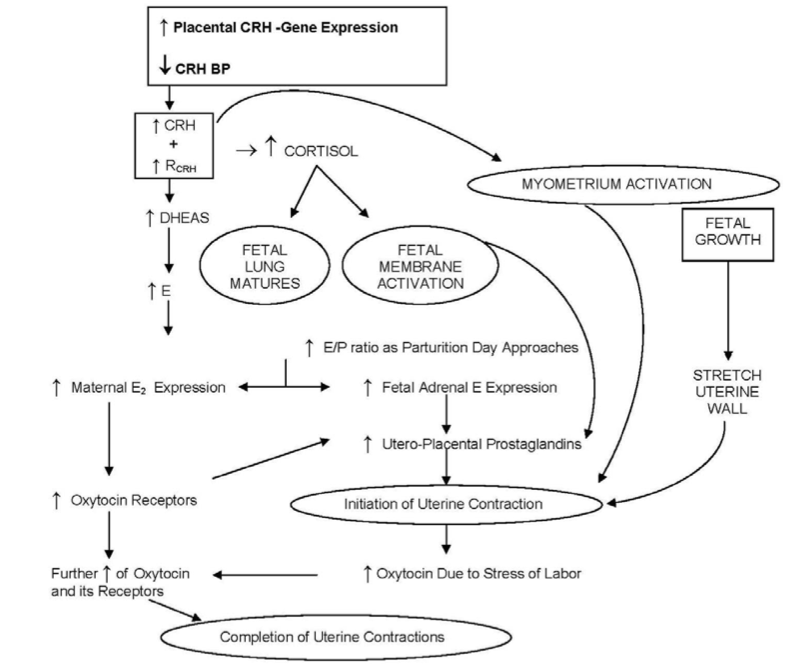
Symptoms—prolonged gestation, poor cervical dilation at the time of parturition and ichthyosis (scaly rough skin) in the newborn

* + - * + Low estriol → low PG, so poor cervix dilation despite Relaxin presence

**ENDOCRINOLOGY OF PARTURITION**

* This is the process of expulsion of the fetus from the uterus. Because of the mortality and sequelae of premature birth, it is important to understand parturition, to be able to minimize prematurity
  + Parturition requires complex changes to move term fetus from inside to outside, to orchestrate proper timing, and to insure maternal and fetal well being in the transition
* Major agents involved:
  + Oxytocin
  + Prostaglandin --↓ collagen content of the cervix and ↑ the water content making the cervix much more pliable
  + Relaxin
  + Progesterone **withdrawal**
  + Estrogen
  + Cortisol
  + CRH
* The peripartum cervical process is as follows:
  + Cervix "ripens" as parturition approaches
    - This means that it becomes softer, more pliable and thinner to permit dilation for passage of the fetus
    - Prostaglandin --↓ collagen content of the cervix and ↑ the water content making the cervix much more pliable
  + Ripening of cervix is due to:
    - Relaxin, a 6,000 MW polypeptide made in corpus luteum and decidua
    - Relaxin functions include cervix softening, pubic symphysis softening, inhibition of uterine  contractions (also renal vasodilation, angiogenesis and increased sperm motility)🡨these all are diff from the effects on parturition
    - Prostaglandin, locally produced, which decreases collagen and increases H2O in cervix
* Control of Parturition is outlined below.

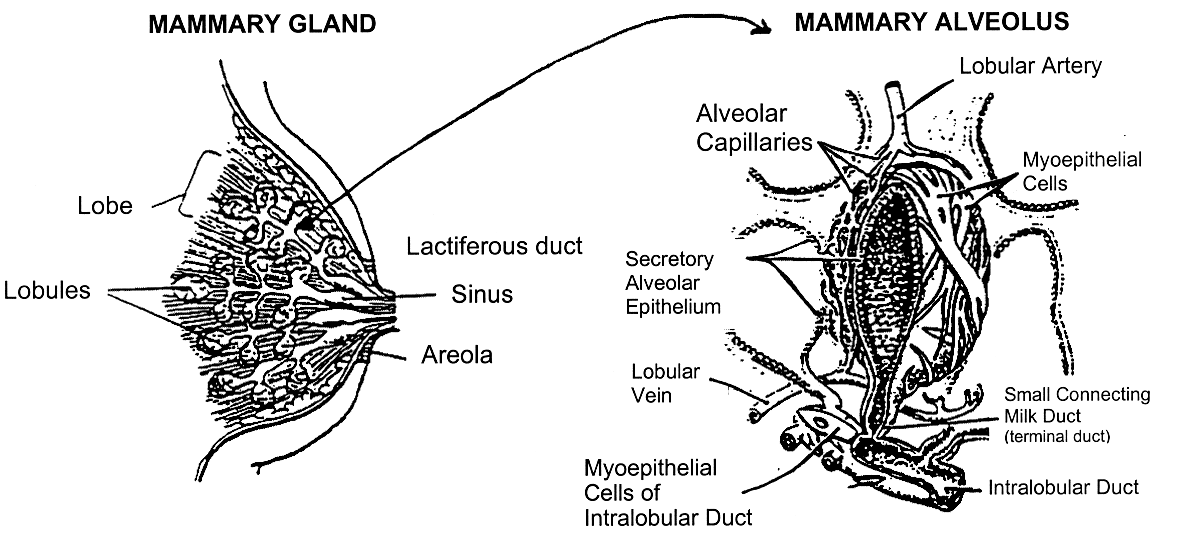
↑ in placental CRH-gene expression and no one knows why this rises. Some think b/c there is a ↓ in P or a change in the P:E ratio favoring E. But onces this CRH gene expression ↑ and ↓ in CRH BP you have ↑ CRH and ↑ CRH receptor competency. Leading to ↑ in cortisol and activation of myometrium. ↑ cortisol causes fetal membrane activation which will lead to ↑ uteroplacental PG’s, ↑ fetal lung maturation (common in prematurity is insufficient lung surfactant production). ↑ CRH also leads to ↑ DHEAS and ↑ E and also ↑ in Maternal E expression leading to ↑ in P:E ratio in favor of E—important as parturition approaches. As the fetus grows it will stretch the uterine wall which will lead to uterine contractions (also earlier you had CRH activating the myometrium and ↑ utero-placental PG’s). ↑ intensity of contractions will lead to ↑ oxytocin due to the increased stress of the impending labor. So you’ll have ↑ oxytocin and its receptors. The Stimulation of maternal E expression also stimulates oxytocin R which all in all lead to completion of uterine contractions.



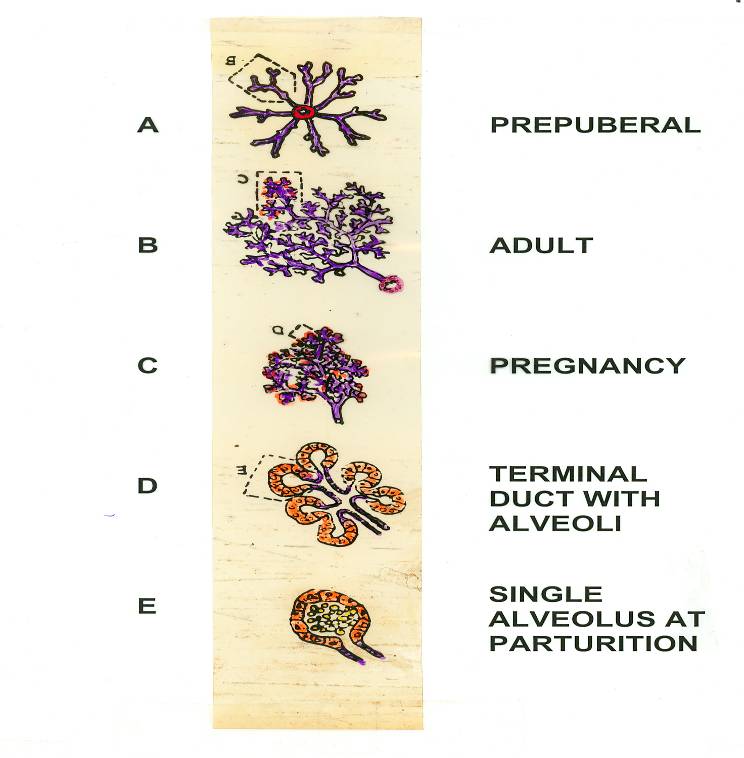
* Parturition Endocrine summary
  + ↑ CRH
  + ↑ Cortisol
  + ↑ Estradiol
  + ↑ PG
  + ↑ Rox—oxytocin receptor
  + ↑ Ox
    - ↑ PG, ↑ Rox (oxytocin receptor) and ↑ Ox all lead to uterine contraction
* Premature Labor
  + Premature labor is similar to normal labor, but having uterine contractions occurring well in advance of normal completion of  pregnancy (before week 37).
    - It is responsible for 85% of neonatal illness and death (high morbidity and mortality) and engenders multi-billion annual costs. Thus, it is important to prevent prematurity when possible.
    - No good treatment for premature labor (nothing lasts >48 hours)
  + Tocolytics (inhibitors of myometrial contraction)
    - Ca++ channel blockers such as
      * MgSO4 with ethanol drip (to inhibit release of oxytocin)
        + Intravenous
      * Nifedipine
        + You have to be careful b/c people can be overactive to this drug or women can have side effects
      * Used to be one of the most common but it has lost its favor in recent years
      * Cannot be used together
    - β-Receptor agonist such as Terbutaline or Ritodrine (relaxes uterus)
    - Oxytocin receptor blocker (limited efficacy)
      * Ex: Otociban
    - Note that CRH monitoring has potential to serve as in indicator of impending prematurity in women at risk.
    - Betamethasone used in premature birth at 24-34 weeks to induce lung maturation (stimulates surfactant production)
      * So if you can stop labor for 48 hours this can help with the lung maturation
    - All of these treatment options temporarily limit the onset of premature labor but nothing lasts beyond 48 hours.
      * Once you start the process of labor it's hard to stop it.
      * But If you know someone is predisposed to prematurity, you must monitor them before this starts. You can put them on these drugs and it won't stop it but it will shut down the process that was starting so that the uterus is no longer irritated and calms down and doesn't contract.
      * Nothing is really really good though :(

**BREAST / MAMMARY GLAND / LACTATION**

**STRUCTURE OF THE MAMMARY GLAND**



* For most women the majority of breast volume is fat tissue. The mammary gland is comprised of a number of lobes distributed in the fat and connected by lactiferous ducts to the nipple, through which milk passes to the exterior. The areola supports the nipple and provides lubrication via small glands (Montgomery glands) within it. The areola and nipple are darker than the rest of the breast due to pigment cells that are influenced by the levels of estrogen and progesterone. The milk producing units (alveoli) of the gland are diagrammed above.
* The mammary alveolus is a hollow sphere of cells made up by the secretory alveolar epithelium of the gland which are the milk secreting cells of the gland. During lactation the hollow sphere of cells in the gland contains milk. Outside of the spheres are specialized myoepithelial cells which are like SM which contract and upon stimulation by oxytocin they will tighten up and squeeze upon stimulation via through the ducts into the nipple where it gets ejected.

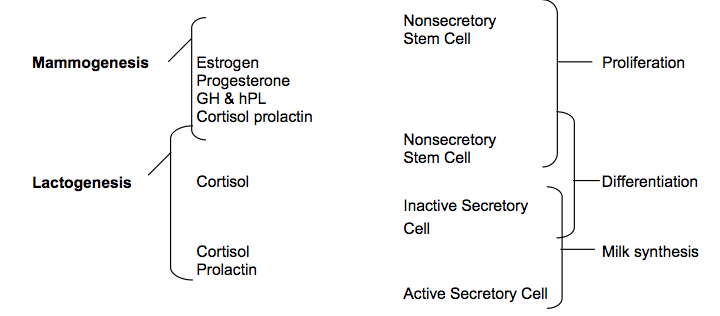
**BREAST CHANGES FROM CHILDHOOD THROUGH MENOPAUSE**

* **Prepuberty**
  + ♂ and ♀ same few short ducts
  + nipple with a few ducts radiating
* **Puberty**
  + ♂ - no change
  + ♀
    - E →↑ ducts + fat deposition (↑ breast size)
    - P →↑ alveoli
    - Ducts begin branching and you see more alveoli from the branches
* **Adult**
  + Menstrual cycle may be assoc. w/ up to 30 cc change in size (max 1-2 days premenses)
* **Pregnancy** - to be discussed
  + The number of alveoli increase A LOT due to progesterone increase
  + Single alveolus at parturition will have globules of milk present inside
* **Menopause**
  + Degenerative changes due to loss of E
    - Loss of Glandular tissue
    - Breakdown of Fat
    - These can be delayed by E Therapy  (HRT)

**HORMONAL CONTROL OF LACTATION**

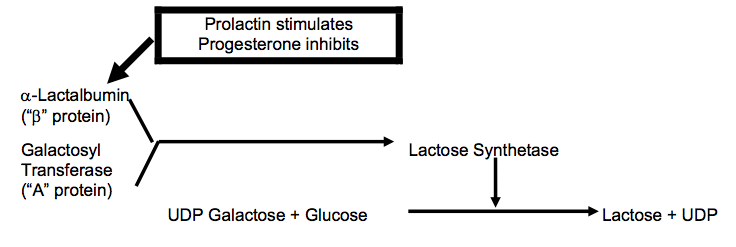
|  |  |  |
| --- | --- | --- |
| **PROCESS** | **TIMING** | **HORMONES** |
| **MAMMOGENESIS (growth of the gland)**   * Ducts, alveoli, growth, vascularity * Initial secretion (Colostrum)-- rich in Immunoglobulins and other nutrients for infant | * Throughout Pregnancy * 2nd Half-- Initial secretory occurs during the 2nd half of pregnancy. | * **Estrogen** --important for ducts * Progesterone --important for alveoli * hPL and GH * Cortisol * Prolactin * T3/T4 and insulin (permissive) |
| **LACTOGENESIS**   * Synthesis and secretion of milk | Beginning at Parturition | * Prolactin * Cortisol |
| **MILK EJECTION**   * Contraction of myoepithelial cells | Beginning with Suckling | Oxytocin |
| **GALACTOPOIESIS (maintanence of the overall process of lacatation)**   * Maintenance of lactation | As long as Nursing is Continued   * Back in the 18th or 19th century women who were "wet nurses” would feed other people's children for years as long as they ate enough and maintained this | * Prolactin * (ACTH) * Cortisol * Oxytocin * Prolactin and ACTH might be called the lactogenic complex in textbooks. The primary job of ACTH is to stimulate cortisol and the prolactin is to stimulate the activity of the milk producing cells |

* **DEVELOPMENT OF MILK-SECRETING CELLS**



* Mammogenesis Occurs all throughout pregnancy
  + You get proliferation of the cells in the mammary glands. Increasing the number of nonsecretory stem cells
* Lactogenesis Doesn't begin until the last half of pregnancy
  + Cortisol allows for the differentiation from the nonsecretory stem cells into inactive secretory cells (capable of producing milk)
  + Cortisol and Prolactin activate the secretory cells and make them active—you get active milk synthesis

**HORMONAL CONTROL OF LACTOSE PRODUCTION**

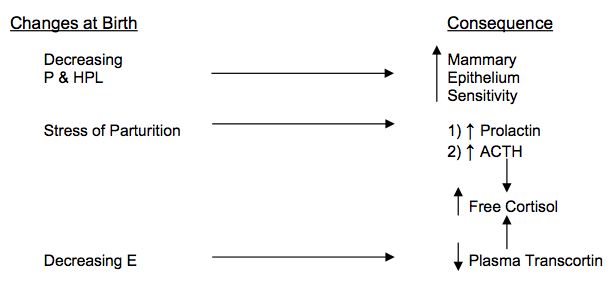


* Stimulation by prolactin and inhibition by progesterone . Their actions are directed at the α lactalbumin portion of the lactose synthase enzyme

**PREPARTUM CONDITIONS WHICH PREVENT LACTOGENESIS UNTIL AFTER PARTURITION**

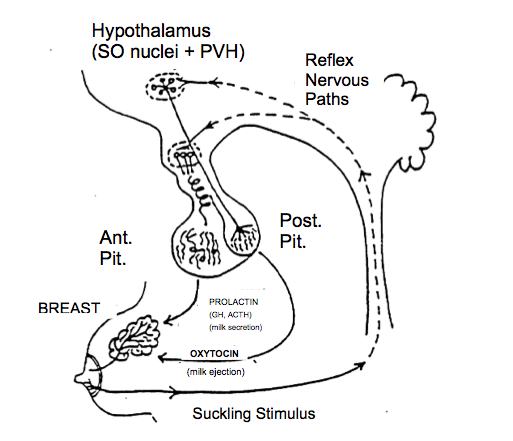
* High P and high hPL levels render mammary epithelium insensitive
  + Mammary epithelium does not produce milk until after parturition because of the high hormone levels during pregnancy.
* Levels of prolactin and ACTH are not greatly elevated
  + the lactogenic complex these hormones are not very increased during pregnancy.
  + Prolactin is only produced just before pregnancy
  + Most of pregnancy these won't be elevated
* The estrogen that's present during pregnancy will cause levels of corticosteroid binding globulin (transcortin) to become very high so the availability of cortisol, which is necessary for the differentiation of cell types that will convert nonsecretory type cells into a secretory type cell, goes down

**INITIATION OF LACTATION**

****

What is changing at the initiation of lactation is that at birth you have ↓ of progesterone and hPL and the mammillary epithelium that is render insensitive by those two hormones can now become active and the stress of parturition itself causes hyperactivity in the pituitary which ↑ the levels of prolactin and ACTH and ACTH ↑ the cortisol and as you go through parturition you have ↓ estradiol which is going to result in ↓ in binding proteins for cortisol which further ↑ the free cortisol levels.

**NEUROHUMORAL PATHWAYS IN LACTATION**



When a baby is born and begins to suckle on the nipple, there is a direct neuronal pathway form the nipple to the paraventricular nucleus in the hypothalamus and it will allow then the release of oxytocin from the posterior pituitary which causes constriction of the myoepithelial cells which surround the alveoli in the mammary gland and also through the suckling stimulis you get activations of the hypothalamus areas involved in production of GH and ACTH and prolactin from the pituitary. They can increase these and stimulate the activity of these milk producing cells.

**MAJOR FACTORS AFFECTING OXYTOCIN RELEASE**

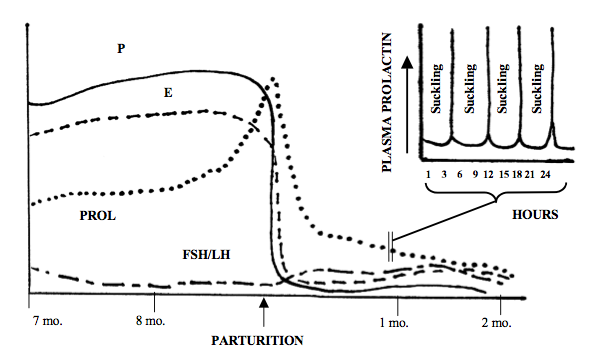
* Normally very low levels
* Increased by
  + Vaginal/cervical stimulation
  + Nipple stimulation
  + (Both pathways are via direct neuronal pathways to the paraventricular nucleus of the hypothalamus)
* Inhibited by
  + Severe anxiety
  + Severe pain
  + Ethanol -- Has been used to shut down the onset of parturition- like in rural areas

**OXYTOCIN ROLES**

* Normally the levels of oxytocin are VERY LOW.
* Uterine contraction
  + key role in partuition
* Myoepithelial cell contraction
  + Key role in milk ejection
* Maternal-infant bonding
  + part of the bottle feeding effect is that you don't get this close bonding not only due to the closeness of holding the baby but also the oxytocin release
* Adult pair bonding
* Decreased anxiety-- it actually reduces anxiety
  + Low oxytocin in autistics (i.e., high anxiety)
  + Oxytocin nasal spray  improves functioning in autistic children
* Behavioral roles (animal studies)
  + facilitates empathy and emotional connectivity in social/sexual/stress settings
  + inhibits feeding behavior
* The process of continued lactation (galactopoiesis) is assured by regular suckling intervals, which cause release of prolactin, ACTH and oxytocin. Release of these hormones is stimulated via direct neural pathway from the nipple to the hypothalamic centers regulating release of these pituitary hormones.

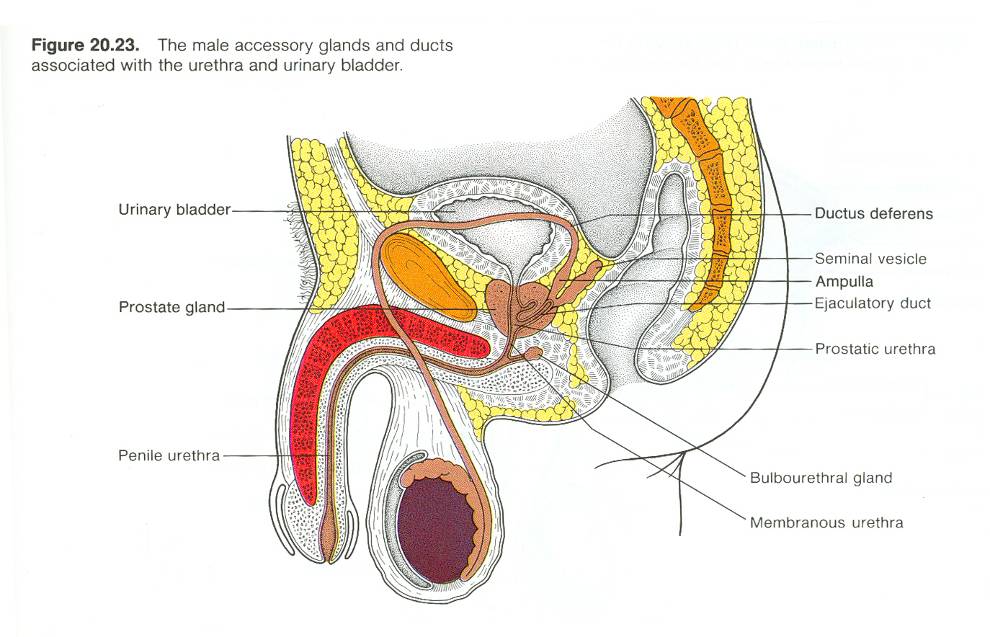
**HORMONE CHANGES BEFORE AND AFTER PARTURITION**

* IN NURSING WOMEN



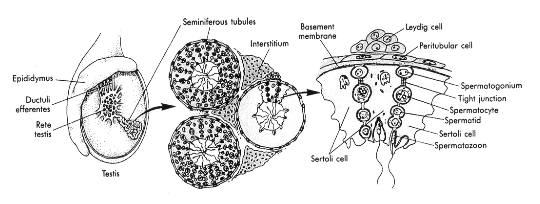
* + In nursing women you have elevated progesterone, estradiol, and prolactin rising close to parturition There is suppressed FSH and LH due to negative feedback. At the time of parturition, the estrogen and progesterone are both dropping off pretty dramatically. The prolactin rises but also eventually drops off even in the nursing women. So what's happening in the ladies who nurse is every time the nipple is suckled, there is a burst of prolactin. This means that this is sufficient to cause the maintenance of lactation but you don't see large amounts in the blood.
    - PROLACTIN CAN INHIBITS FSH AND LH RELEASE!!!! So it can limit ovarian and follicular development so it can actually serve as a contraceptive in lactating women. But b/c the prolactin is released in bursts its different than prolactin being constantly around so this doesn't really work well though. In 50% of cycles ovulation still occurs.
* IN NON-NURSING WOMEN
  + If nursing does not occur, hormone pattern returns to normal menstrual cycle, usually within 1 month.
  + If mother does not want lactation to occur, it is important to not stimulate the nipple. If engorgement does occur, a support bra with ice packs is helpful.
    - If you wait a period of time 4-6 weeks then the engorgement will gradually disappear and they will get their periods back, etc.
  + High-dose pyridoxine can be used for up to 7 days to suppress prolactin by increasing dopamine. Androgens, estrogens and bromocriptine previously used as lactation suppressants, but are all currently off the market due to side effects.
* FACTORS AFFECTING NURSING SUCCESS
  + Psychological stress can inhibit lactation
    - Via ↑ epinephrine 🡪 ↓ oxytocin
    - Via ↑ sympathetic activity inhibiting mammary blood flow
  + Oxytocin injection can restore the milk release
  + Ethanol 🡪 ↓ oxytocin release
* BREAST FEEDING VS. FORMULA FEEDING
  + Breast feeding generally favored because:
    - Most natural infant food
    - Colostrum is immunoglobulin - rich
    - Lower morbidity and mortality
    - Better mother - child bonding
    - stronger maternal drives from oxytocin
    - Acts as contraceptive? Generally NO.
      * With proper training you can actually use this and it's pretty effective!
      * unless nursing bouts are regimented (consistent intervals) to insure regular prolactin spikes that tonically inhibit FSH/LH release, ovulation can occur in 50% of cycles.
      * for more info: Google “family planning initiative LAM”

**MALE REPRODUCTIVE PHYSIOLOGY**



**MALE REPRODUCTIVE TISSUES**

* The male reproductive tract consists of:
  + the testes (which produce germ cells and hormones),
  + prostate and seminal vesicles (primary producers of seminal fluid, with minor contributions by Cowper’s (bulbourethral glands)
  + and a tubular system for sperm storage and transport consisting of epididymis, vas deferens, ejaculatory duct and urethra.
    - The vas is the major portion of this path.
    - The ejaculatory duct is a 2 cm portion of the vas passing thru the prostate where it joins the seminal vesicle duct.
    - The urethra consists of posterior (prostatic, membranous) and anterior (bulbar, penile, navicular) segments.
* **The testes**
  + Migrate into scrotum during fetal development.
  + Temperature in scrotum is about 2C lower than body core, facilitating spermatozoa production.
    - This temperature difference is pretty critical in sperm development
  + Major compartments are:
    - Seminiferous tubules (80% of testis volume), a mass of coiled loops serving as the site of spermatogenesis the sperm then travel into the core of the testis is known as the Rete testis 🡪 then into the ductuli efferentes which connects the seminiferous tubules to the epididymis and then leaving the epididymis it becomes the vas deferens (may contain spermatozoa depending on the rate and production of sperm)
      * Large Sertoli cells in the seminiferous tubules are closely involved in hormonally directed  spermatogenesis.
      * Sertoli cells (very large cells that make up most of the internal area of the seminiferous tubules) are also the source of several important proteins that are essential for normal  male functions:
        + Androgen Binding Protein (ABP) (intratesticular, not found in the plasma)
        + Inhibin/Activin—intragonadal regulation related to the production of germ cells (sperm & egg) by regulation of FSH (needed for oogenesis & spermatogenesis)
        + Müllerian Inhibiting Substance (MIS)
    - Interstitium (connective tissue) between the tubules, which contains **Leydig cells** that produce androgens and they are under the control of LH
  + Diagram of testis and its compartments



In between the Sertoli cells (aka nurse cells) you have germ cells developing. They are the key cells in guiding the process of spermatogenesis

* Epididymis and Vas Deferens
  + Testis is continuous with the *epididymis*, a tubular storage/maturation site for spermatozoa.
  + Sperm leaving the epididymis travel through the tubular *vas deferens* to reach the *ejaculatory*  *duct* and *urethra* for ejaculation.
* Bulbourethal gland (aka Cowper’s gland)
  + Pea-sized; producing clear lubricating fluid during sexual arousal that washes/dilutes urine from urethra before ejaculation.
* Prostate and Seminal Vesicles --both located at the distal end of the vas deferens
  + These are the sources of *seminal fluid*, first contributed by the prostate and then by the seminal vesicles, both located at the distal end of the vas deferens.
    - 60% of the volume of seminal fluid is from seminal vesicles
    - 20% of the volume of seminal fluid is from prostate
    - Remainder is from other secretions along the male tract as the sperm moves through it
    - Seminal fluid functions
      * Transport medium for spermatozoa
      * Nutrient medium for spermatozoa
      * Chemical protection of sperm—they ↑ pH generally above 8 b/c the sperm don't like acidic environment
      * Contains hormones—not produced by the prostate or seminal vesicles but produced elsewhere
        + FSH, LH, Prolactin, T, E
        + Activin, Inhibin, Oxytocin, Endorphin,Relaxin
        + The function of most of these hormones is related to spermatogenesis but some are involved in contraction of myometrium when the semen is present in the female
        + Endorphins are involved in the process of normal fertility
        + Relaxins is present and may or may not contribute to some physiology but we don't know
  + Seminal vesicle provides
    - Fructose (sperm energy)
    - Prostaglandins (stimulate ♀ tract contractions while sperm move through the female tract)
      * This along with the sperm motility help move the sperm along
  + Prostate provides
    - Spermine (responsible for semen odor and alkalinity) –is responsible for the alkalinity that is needed for proper sperm survival
    - Citric acid (retards coagulation) –it's the proportions of this to calcium that determine whats going on. In the female reproductive tract you want more calcium so ↑ coagulation and in the male reproductive tract you want more citric acid so ↓ coagulation of semen
    - Calcium (aids in semen coagulation)
    - Zinc (↑ sperm vigor/ quality)
    - Acid phosphatase (sperm phospholipid metabolism) also is used as an indicator in cases of rape to show semen has been deposited in a female but it was found that females produce small amounts of this so using this for rape may not be very reliable
    - Relaxin (enhances sperm motility) –not sure how critical this is
    - FPP (fertilization-promoting peptide)—plays a role in enhancing motility around the time of fertilization/capacitation of sperm
    - PSA (prostate-specific antigen) also used to check for prostate cancer in male and also is used in cases of suspected rape
  + Both tissues are controlled by androgen.
    - Androgen stimulates growth and can produce hyperplasia (BPH) and cancer, with production of a  *prostate-specific antigen (PSA),* which is an IGF-BP protease). PSA is used in screening for  prostate cancer and as vaginal test for rape.
    - Androgen effects are augmented by prolactin (mostly in prostate not so much in the seminal vesicles).
      * So think about this when you have a person with prostate cancer
  + Prostate Disorders
    - Benign Prostatic Hyperplasia or Hypertrophy (BPH)
      * Not really a disease, rather a normal part of aging
      * Due to T 🡪 DHT 🡪 leading to Prostate growth
      * After age 50-60, ↑ aromatization (more E🡪 stimulates the ↑ androgen R 🡪 renewed prostate growth)
      * Can be limited by Finasteride (5α-reductase inhibitor)
      * 20% of individuals exhibiting BPH symptoms get prostate cancer
      * BPH symptoms include ↑ urination frequency, poor stream, extensive dribbling after urination is completed
        + This is in part due to a reaction by the SM of the detrusor mm that becomes more active and closes down the pathway in response to BPH
        + You can use an α-adrenergic blocker to relax this SM and enable better urine flow
    - Prostate cancer
      * Cause of 10% of all cancer deaths in males
        + 3rd most prevalent male cancer (Lung 1, Colon 2)
        + 2 types

Slow growing

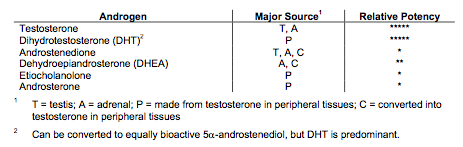
Aggressive growing (only 1-3% of people will develop this)

* + - * PSA screening can help for slow-growing type, but aggressive type already advanced by  time screening shows it.
      * BPH can give false high PSA, so a biopsy is the best definitive test.
      * If you do surgery on the prostate you can damage the ejaculatory duct and if that happens then the person could get retrograde ejaculation and wont be able to have normal ejaculation
      * DHT facilitates the carcinogenesis, but it is not by itself carcinogenic it just is a potent androgen that is stimulating whatever cells will respond to it
        + Can be limited by Finasteride (5α-reductase inhibitor)—inhibits the production of DHT so you can limit the rate of growth of cancer in the prostate
        + Estrogen (this is pharmacological situation not the physiological one we discussed previously) can be used for treatment to suppress androgen production—it does this by inhibiting gonadotropin production its negative feedback effect is the main reason estrogen at pharmacological levels is effective in suppressing prostate cancer b/c it ↓ androgen production by the testes

Physiological is more E🡪 stimulates the ↑ androgen R 🡪 renewed prostate growth

**ANDROGENS**

* Androgens are steroids and are made primarily by the testes, but some by the adrenal cortex (in the female this is what is more important for androgen production)
* Androgen bioactivity differs among the various androgens and the two most important and potent androgens are testosterone (T) and dihydrotestosterone (DHT).



* Estrogens (17β estradiol and estrone) are present mostly from peripheral conversion of testosterone and androstenedione but play a minimal role.
  + But as the male ages there is ↑ aromatization so you get ↑ estrogens present and playing a role (more E🡪 stimulates the ↑ androgen R 🡪 renewed prostate growth)

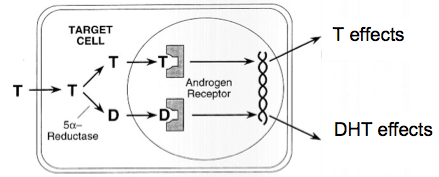
**PHYSIOLOGICAL EFFECTS OF ANDROGENS**

* Categorized as androgenic (sexual function related) or anabolic (metabolic related).
  + Androgenic (associated with sexual function)
    - Stimulates spermatogenesis
    - Stimulates libido
    - Growth of male tract - ducts, accessory glands, penis & scrotum
    - ↑ Body and face hair and baldness
    - ↑ Vocal cord thickness
    - ↑ Sebaceous gland secretion (both sexes)
  + Anabolic (examples)—metabolic function
    - ↑ Bone growth and epiphyseal closure
      * Both androgens and estrogens stimulate epiphyseal closure but estrogens are more effective than androgens which is why females are generally not at tall as males
    - ↑ Muscle mass and strength—this is the reason for black market of anabolic steroids
      * Androgens are acting directly on the muscle but you have to realize that the androgens are stimulating IGF-1 to some extent b/c it is necessary for heavy anabolism
      * It also limits the effects of catabolic cortisol actions
    - ↑ Protein anabolism

**PHARMACOLOGICAL EFFECTS OF ANDROGENS**

* Anabolic steroids
  + Only for use under medical supervision
  + Large black market use nonetheless
    - Anabolic Steroid Control Act (2004)
    - Banned most synthetic anabolics, so a natural steroid “prohormone” market developed  in private sector
    - ‘prohormones’ such as 19 -Nor testosterone made in body in small amts., so synthetic version of it  can be used (e.g. Durabolin, Decadurabolin).
    - In 2011 they added more limitations of designer anabolics
  + Many adverse side effects (especially with synthetics), including
    - Inhibition of gonad function –spermatogensis can be impaired and endogenous androgen production impaired
    - Gynecomastia –development of breasts in males
    - Liver disease –liver enzyme systems that deal with these anabolics become compromised and the liver becomes dysfunctional and it can lead to death
    - Coronary artery disease
    - Impaired adrenal axis—can feedback negatively and inhibit adrenal function. This can impact the individuals ability to handle stress and in a chronic situation (which is how these anabolics are used) it can screw up normal homeostasis
    - Masculinization of females
* Androgen treatment of andropause
  + Has become significant clinical issue
  + >4 million users among estimated 10 million T-deficient males in U.S., with >10 x increase in use 1998-2010
    - doesn't have to be prescribed by a physician
  + Less dangerous (lower doses) than anabolics, but long-term effects unknown

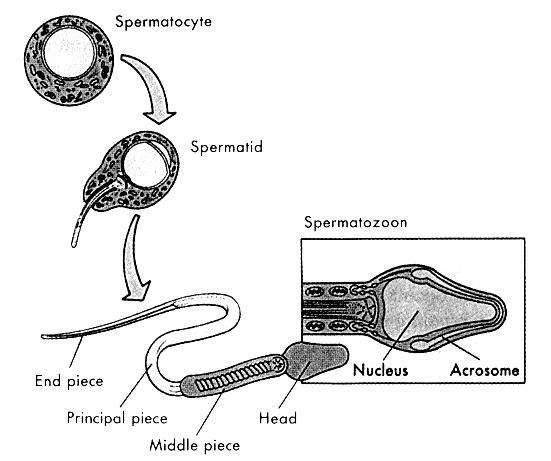
**MEDIATION OF ANDROGEN ACTION**

* In some cells, T acts directly. In other cells T must be converted to DHT to act. T effects  DHT effects
  + 
* T enters the cell and binds to a receptor in the cytoplasm or in the nucleus and if there is 5α Reductase present you will get DHT which will attach to the androgen receptor and if there is not enzyme then T will bind to the androgen receptor
* The same androgen receptor binds both T and DHT, but *DHT binds 2x more avidly*.
* Most DHT is due to intracellular conversion from T. Plasma T:DHT ratio is 10:1 (little DHT in blood/peripheral circulation).
* Remember that testosterone (not DHT), especially in excess, can also be converted by aromatase to bioactive estrogens.
* 5α-Reductase converts T → DHT
  + All androgen sensitive tissues contain 5 α-reductase
  + Level of this enzyme in given tissue determines if T or DHT is the primary effector.
* Androgen actions due directly to T are:
  + Gonadotropin feedback regulation
  + Spermatogenesis
  + Skeletal muscle growth
  + Bone growth
  + Fetal internal reproductive tract virilization
    - T alone cant give males normal internal reproductive tract development—they need Mullerian inhibiting substance (MIS) to prevent female tract development
* Androgen actions due directly to DHT are:
  + Prostate development
  + Seminal vesicle development
  + Fetal external genitalia virilization (masculine)
  + Sexual maturation changes at puberty

**SPECIFIC BINDING PROTEINS ASSOCIATED WITH ANDROGENS**

* **IN PLASMA**: Testosterone Binding Protein (TeBG) = (SHBG) is a 95,000 M.W. glycoprotein. Specifically binds 44% of circulating T.
  + TeBG levels in women are 2-3X higher than in men.
  + Albumin binds about 54% of T (weakly), and 2% is unbound.
  + T and DHT also bind to SHBG (Steroid Hormone Binding Globulin)
* **IN TESTIS**: Androgen Binding Protein (ABP) is a glycoprotein similar to TeBG, but is made by Sertoli cells (so w/in the testis). ABP Binds T and DHT in seminiferous tubules, insuring high local concentrations of these hormones to accommodate spermatogenic process.
* **MALE VS. FEMALE**: Both TeBG and ABP will bind E, but with less affinity than T.
  + This fact and the higher TeBG levels in women account for significant sex differences in T and E delivery to tissues.
    - Ensures that more estrogen than androgen effects will occur in a female

**SPERMATOGENESIS**

* Sperm
  + Head—has a bilayer with an internal membrane and external membrane and between the two is the acrosome and that contains critical enzymes which are involved in fertilization allowing the penetration of sperm into the egg.
* A continuous process throughout male lifespan
  + Spermatogonia (primary germ cells), unlike oogonia, replicate by cell division
    - First step in oogenesis is meiosis not mitosis
  + 100-200 million sperm produced daily
  + 1 spermatogonia 🡪 64 spermatozoa
  + A spermatogenic cycle is 60-70 days 🡨this is one of the main reasons male chemical contraception has had very little success because its such a long process
  + New waves of spermatogonia enter the cycle every 16 days
    - So continuous and overlapping process
  + Several waves are in progress simultaneously
* Division sequence –this whole process is being guided by Sertoli cells
  + Spermatogonia undergo diploid mitosis to spermatocytes
  + Spermatocytes undergo meiosis to haploid spermatids
  + Spermatids are haploid sperm precursors
  + Spermatids undergo maturation process to convert to sperm

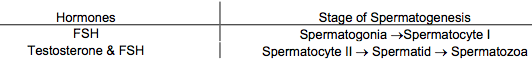
**SPERM STORAGE AND RELEASE**

* Spermatozoa take 2-4 weeks to traverse the *epididymis* to the *vas deferens*, and during that time they become motile and lose their cytoplasm. About one ejaculate (200-400 million sperm) of sperm is in the epididymis at any time.
* Sperm in the vas deferens are viable for several months (capable of motility w/ minimal cytoplasm), and are delivered from there to the outside by the process of ejaculation.
* The ejaculate
  + One ejaculate contains 200-400 million sperm in 2-4 cc.
    - So you have 1 ejaculate stored, another ejaculate in the epididymis and if you keep ejaculating you need at least 2 days to replace the amount (only 100-200 million are produced each day). Continual ejaculation will result in ejaculate with ↓ sperm count and ↓ volume
  + Considerable volume variation across men
  + Volume and sperm count reduced by multiple ejaculations
  + Old age yields decreased volume (>60)
* Ejaculate normalcy criteria
  + >60 million sperm
  + >60% motile with forward movement
  + >60% have normal morphology
  + \*\*so think of it like 40% can be abnormal and the male can still be fertile

**MOTILITY, CAPACITATION AND GAMETE SURVIVAL**

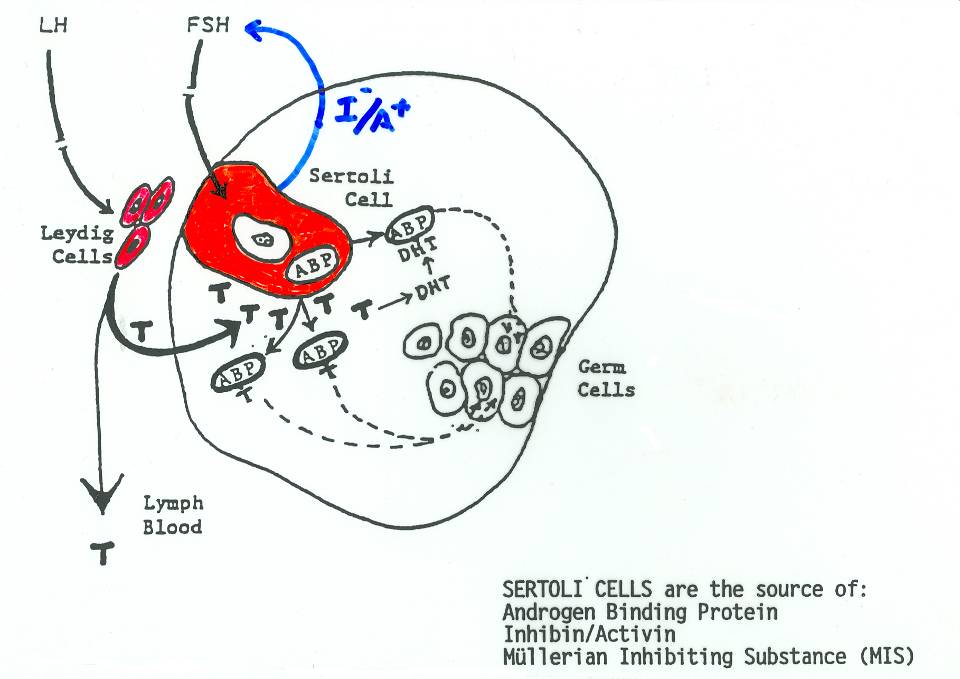
* Sperm *motility* increases dramatically in the female tract, but to transport the ovum requires smooth muscle contractions of the female tract (some of this is stimulated by things-like oxytocin- in the semen)
  + Once sperm are deposited at the base of the cervix the motility ↑ very dramatically
* Sperm lifespan in the female tract is about 48 hours; egg lifespan is 6-12 hours once its ovulated
* Once the sperm and the egg are in close proximity to one another several things must occur for fertilization to happen:
  + **Capacitation** (this is even before the sperm gets close to the egg)
    - Sperm must undergo a 4-6 hour process of *Capacitation* within the female tract before they can fertilize an ovum.
      * So 4-6 hours after its deposited at the base of the cervix until it can fertilize an egg
    - Involves changes in sperm surface characteristics and optimization of fertilization promoting peptide (FPP) levels to allow onset of good motility needed for sperm to fertilize the egg
  + **Sperm activation** 
    - Consists of ***Hyperactivation*** and ***Acrosome Reaction***, which occur when sperm is in proximity  to egg
    - *Hyperactivation* 
      * A marked increase in sperm swim speed with more forceful and erratic tail whip. These ↑ probability a sperm will fertilize an egg
    - The *Acrosome reaction* 
      * Initiated when sperm binds to zona pellucida (ZP) protein
      * Acrosomal membrane and outer sperm membrane fuse, permitting escape of hydrolytic and proteolytic enzymes which aid sperm penetration of the egg.
  + **Fertilization** 
    - Sperm-egg fusion
    - Activation of final stage of egg meiosis
    - Activation of egg metabolism
    - Prevention of polyspermy, which is lethal

**HORMONAL CONTROL OF SPERMATOGENESIS**

* Repeated, pulsatile-release of GnRH is necessary to begin the process.
  + This is also necessary to ovulation of the female but in the male these pulses are very low grade compared to the female
* ↑ GnRH also leads to ↑ FSH acts on the seminiferous tubules directly initially to stimulate early stages of spermatogenesis
* ↑ GnRH leads to ↑ LH which stimulates Leydig cells to produce testosterone, which then acts on the seminiferous tubules
* 
* Other factors which influence spermatogenesis–all of these things play a role w/in the Sertoli cell which enable and continue spermatogenesis
  + Vitamin A
  + c-fos (a nuclear protooncogene)
  + Stem cell factor
  + c-kit receptor for stem cell factor
  + cAMP-response element modulator (CREM)

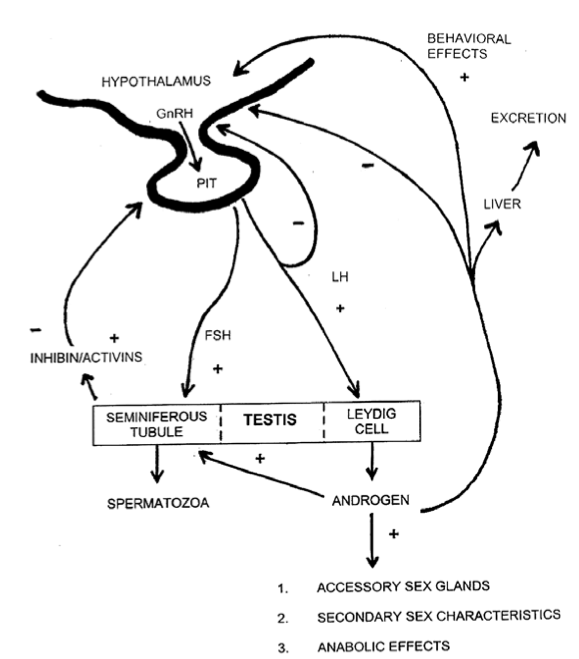
**TESTICULAR REGULATION**

* Androgen
  + Mostly T, some DHT
  + Supports later stages of spermatogenesis
    - By acting on Sertoli cells
      * Synergizes with the FSH to Upregulate Sertoli T receptors
      * Upregulate Sertoli ABP production which will assure whatever T is present will stay in the vicinity of the Sertoli cells and be available to enable the androgenic effects on spermatogenesis
      * ↑ N-cadherin (membrane protein)
        + ↑ Spermatid binding to Sertoli cells (enhances spermatogenesis)
* Inhibin and Activins
  + Inhibin is a 3-subunit protein hormone produced by the Sertoli cells in males and granulosa cells in females.
    - It specifically **inhibits pituitary FSH** (but not LH) release.
    - Release locally inhibited by androgen and E.
  + Activins consist of 2 of the 3 subunits of inhibin and act primarily to **stimulate pituitary FSH release**.
    - Also locally blocks androgen and E synthesis.
    - This hormone is also made by ovarian granulosa cells and has similar action in the female as in the male.
  + Their importance is in providing a gonad-specific feedback loop for regulating gamete production, i.e., a loop that tunes in to the **gamete-producing** (rather than steroid-producing) role of the gonads. Its specific for FSH which regulates gametogenesis in both females and males



* Prolactin
  + Normal levels
    - Upregulates androgen receptors in prostate
    - Upregulates LH receptors in Leydig cells
  + Excess levels (e.g., pituitary tumor)
    - ↓ FSH and LH
    - ↓ Androgen
    - ↓ Spermatogenesis
    - ↓ Libido

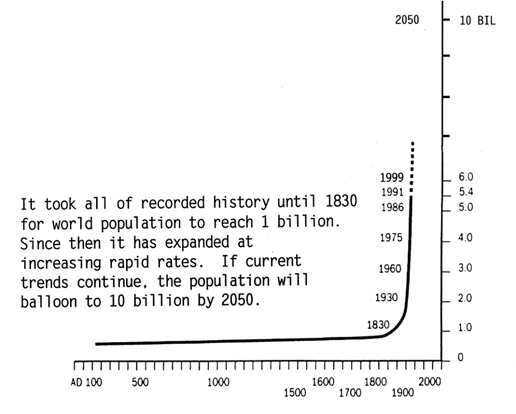
**HYPOTHALAMIC-PITUITARY GONADAL AXIS IN THE MALE**



GnRH in the hypothalamus stimulating the pituitary to make FSH and LH. In the Testes the FSH in the seminiferous tubules stimulating spermatogenesis. Feedback loop through the Sertoli cells producing activin and inhibin to regulate the FSH. The FSH release stimulates the LH release from the anterior pituitary and it works on the Leydig cells which release androgens. These androgens work with the FSH to help stimulate later stages of spermatogenesis. Androgens also stimulate secondary sex characteristics and have anabolic effects. In the CNS androgens can produce changes in aggressive behavior and sexual drive. Androgens also have negative feedback on GnRH.

**CONTRACEPTION**

* **INTRODUCTION**
  + Because many people use contraception and many means of contraception are available only through physicians and because much misinformation exists in the public sector on this topic, it is an important part of medical training.
  + From another perspective, it is estimated that in October 1999 the human population reached 6 billion, with the next billion expected well before 2030 at the present growth rate.
  + It is likely that future efforts to balance natural-resource availability with population demand will place increasing emphasis on contraception and therefore on the medical community to enable its use safely and intelligently.
* **HUMAN POPULATION GROWTH**



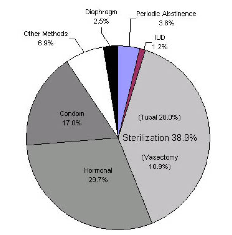
One thing that really allowed this population to rise so drastically after 1830 was the discovery of penicillin which ↓ disease. In the past 50-60 years we have discovered SO MANY more drugs that help keep people alive longer.

|  |  |  |  |
| --- | --- | --- | --- |
| **% OF COUPLES USING CONTRACEPTION** | **1965** | **1993** | **2011** |
| **Number of Children per woman** | **6/1** | **3.7** | **3.4** |

**IMPACT OF CONTRACEPTION IN DEVELOPING COUNTRIES**

* Effects of reduced population growth include:
  + Improved food supply
  + Less habitat destruction
  + Better air/water quality
    - Air quality in China have become so bad that the toxicity of the air has become so bad that some people have to wear masks in order to just walk on the streets.
    - Effects of overpopulation include increased:
      * Lead and Mercury
      * Asthma and Allergies
      * Emphysema
      * Cancer
      * Stress-related disorders
  + Better health and quality of life for humans and other species

**CONTRACEPTION IN THE USA**

* Contraceptive education is inadequate. A 1999 National Geographic Study reported that 40% of American women have been pregnant once by age 20.
  + ↑ in education and ↑ use of contraception has really helped lower the incidence of teen pregnancy in the USA (even thought the USA still has the highest rate of teen pregnancy but the numbers are ↓)
* Contraceptive use in 2006 presented as percentage of total users.
* Sterilization is the most common used contraception/fertility control in the USA. This is done by couple who already have their families and don't want any more kids. Next is hormonal contraception (pill, implants, and injectables, and androgens). Next largest use of contraception is condom (↑ use w/ ↑ education about HIV)
* **NOTES:**
  + “Other methods” include female “barrier”, sponge, spermicides-only.
  + “Hormonal” includes oral pills, progestin, depot injection, subdermal implant.
  + “Periodic Abstinence” includes calendar rhythm method, NFP (Natural Family Planning).

**CATEGORIES OF CONTRACEPTIVE ACTION**

* Prevent ovulation –major means by which oral contraceptives containing estrogen work
* Render female tract inhospitable to sperm transport/survival –when you have a progesterone dominant environment it is inhospitable for sperm transport and survival—this is the basis for which a progestin only type pill was formulated
* Prevent implantation
* Inhibit spermatogenesis –this has a lot of potential but remember that the whole spermatogenesis process takes 60-70 days. Anything that inhibits spermatogenesis will likely inhibit any androgen stimulated behavior. So if used in a male they would have to take androgens to supplement for this and allow normal male patterns of behavior.
* Physical barrier—diaphragms, cervical caps, condoms
* Spermicide
* Surgical/chemical sterilization
* Forms of abstinence

**ESTABLISHED CONTRACEPTIVE METHODS**

* Oral E and P (the pill) --most popular of all contraceptives in this country
  + Primary action is to prevent ovulation by providing continuous estrogenic negative feedback to  the hypothalamus, (blocking the hypothalamic-pitutiary-gonadal axis and thereby inhibiting GnRH and gonadotropins) thereby preventing the preovulatory LH surge needed for ovulation—prevents the ovary from having normal follicular growth
  + Several varieties (>70) and doses of daily pill available (20-50 g E and 0.5 mg P).
  + All present day contraceptive steroids are synthetics, modified to enhance activity or duration  (commonly **Ethinylestradiol** and Levonorgestrel--progesterone).
    - Much longer t1/2 life than physiological E or P—can last in the body for weeks after they are released and are harder to break down
* Progestin-only (commonly Norgestrel or Norethindrone)
  + Primary action is to interfere with sperm transport/survival
    - Inhibits ciliary activity, secretory activity in the uterine tube and both these things ↓ movement of sperm. It also creates thicker cervical mucous, ↓ pH, etc.
  + Secondary actions
    - Render endometrium hostile to implantation
    - Prevent ovulation (about 50% of cycles where it is present)
  + Daily dose range 0.5-1.0 mg
    - Pharmacological levels
  + Several formats used
    - “Mini” pill (oral)—because only progestin (no estrogen)
    - Depot injection
    - Subdermal implant—norplant—no longer available in the USA
    - Patch (usually E+P but also P-only)
    - Vaginal ring (usually E+P but also P-only)
    - IUD (Mirena ®), contains Levonorgestrel
      * Plastic that also contains progestin (levonorgestrel)
  + Useful for women who have side effects from estrogen-containing pill
* Androgens
  + inhibit spermatogenesis
  + low incidence of use due to initial 2-month delay in effectiveness and behavioral side effects of suppressing the androgens
    - now they are using progesterone to limit the production of sperm and giving the patient androgens to make up for the limitation of endogenous androgen production
* Intrauterine device (IUD)
  + Induces invasion of leukocytes b/c there was a foreign object in there, thereby preventing implantation
  + Troubled history (1970’s/80’s)
    - IUD ejected without woman noticing
    - Uterine wall punctures—b/c it wasn't places properly
    - Infection –because the string hanging out of the cervix was used as a pathway for bacteria so they started putting antibiotics on the string
  + Current IUDs –interfere with fertilization. They act before implantation.
    - Greatly improved, excellent track record
      * More flexible and soft
    - Copper IUD most used (ParaGard ®, note: copper impairs sperm motility in the uterus)
    - Intrauterine System (Mirena®), IUD containing levonorgestrel)
    - Still the least-used contraceptive type especially in the USA
* Barriers
  + Condom (male/female)
    - Condom use has increased dramatically in recent years, since it prevents HIV transmission as well as providing contraception
      * ↓ sensitivity of the penis and ↓ the enjoyment level of both partners
      * 28% of males have trouble maintaining an erection when wearing a condom
    - Diaphragm
    - Cervical cap
      * The diaphragm and cervical cap have reasonable contraceptive use if they are effectively applied but because it is kind of difficult and most people want to just get on to the sex part they dont apply it correctly so there is a lot of failure with these
* Spermicide
  + A foam injected into vagina near cervix
  + **Nonoxynol-9** is most common agent
    - destabilizes sperm membrane (surfactant) –very effective at killing sperm
      * problem is making sure it is actually applied at the base of the cervix
    - Excess use causes
      * ↑ yeast infection
      * Vaginal/penile irritation
  + Best used in combination with condom or diaphragm (another barrier method)
* Surgical/chemical
  + MALES
    - Vasectomy (male) –cut the vas and tie off the two ends. There is an ↑ in prostate cancer associated w/ this
    - Vas deferens blockage
      * By transcutaneous cyanoacrylate injection (crazy glue)—causes incredibly powerful bonding of the skin to itself. Originally they would use this crazy glue during war times to close wounds in transporting soldiers on the field to a medical field hospital.
  + FEMALES
    - Tubal ligation (female)
    - Tubal blockage of uterine tubes
      * transcervical cyanoacrylate injection
      * transcervical insertion of metal coil/polymer (Essure) into the uterine tube
        + blocks transport
      * heat/polymer placement (Adiana)—fuses and expands and blocks the path in the uterine tubes
  + The above methods are irreversible (sterilization), most commonly used by couples who  already have children
* Abstinence
  + total (celibacy)
  + partial (no intercourse)—oral sex is allowed
  + Periodic
    - Calendar Rhythm Method works only for women with very regular cycles
      * Female makes use of their menstrual cycle and determines when there is a safe period during the cycle for intercourse. Look at when the last menses was (and if you know when the last ovulation was) and then you move forward from that for X amount of time when there is a safe period before ovulation begins.
    - Natural Family Planning (NFP); a method that can be very reliable, since it monitors  physiological changes during the cycle
      * Based on concept of a “safe” period for unprotected intercourse in each  cycle
      * Monitors menstrual cycle patterns of
        + Basal body temperature

The change in this during the cycle is due to (before ovulation occurs there is a slight ↑ in progesterone b/c of the early conversion of some of the cells in the cell population from granulosa🡪 lutein type cells. This ↑ increase in progesterone is recognized in the CNS thermoregulatory centers leading to an ↑ in basal body temperature (1/2🡪 1 degree). In a period that monitors their cycle they can see it in every cycle and it tells them that ovulation has occurred in the cycle.

* + - * + Cervical mucous production and quality

Difference in cervical mucous conditions in an estrogen dominated environment and a progesterone dominates environment.

* + - * + Cervix condition
      * Non-drug; non-barrier
      * 1-5% failure rate with proper use
      * Requires 7-10 continuous days without intercourse per cycle
      * Fits self-awareness/self-care paradigm of ‘wellness medicine’
        + Because you pay more attention to yourself and your body
      * Most applicable to long-term relationships

**APPROXIMATE FAILURE RATE**

**(PREGNANCIES PER 100 WOMAN YEARS)**

* Contraception can occur via actions on the hypothalamic-pituitary system, the ovary and female tract, or testis and male tract, or on sperm and ovum directly. The table below lists failure rates for the most commonly used birth control methods reported in 2009.

|  |  |  |
| --- | --- | --- |
| **Approximate Contraceptive Failure Rates** | | |
|  | **Correct-Use FAILURE** | **Typical-Use FAILURE** |
| Celibacy | 0 | 0 |
| Tubal Ligation | <0.1 | <0.1 |
| Vasectomy | <0.15 | 0.15 |
| IUD (Cu++ or Progestin) | <1—only use bc physician puts it in | <1 |
| Long Acting P\* | <1 | 3 |
| Oral Contraceptives (E + P\*) | <1 | 5-8—b/c the women aren’t taking the pills correctly |
| Condom + Spermicide | 1 | 5-10 |
| Low-Dose Oral P\* | 1 | 5-10 |
| Natural Family Planning | 1-5 | 16-20—they aren’t paying enough attention or the woman’s cycle is so variable |
| Condom Alone | 3 | 15-20 |
| Coitus Interruptus-withdraw of penis at the time of ejaculation | 4 | 27 |
| Diaphragm + Spermicide | 6 | 16 |
| Rhythm (Calendar) | 15 | 25 |
| Spermicide Alone | 6 | 26 |
| Lactation for 12 Months—50% of the time ovulation still occurs | 10-15 | 40 |
| Chance (sexually active) | 85 | 85 |
| \*\*P = progestin (e.g., levonorgestrel) | |  |

* + - * + note: data for failure rates vary greatly across reporting sources
        + anything w/ a failure rate >6% is considered unreliable

**SIDE EFFECTS OF HORMONAL CONTRACEPTIVES**

* There is great variation in responsiveness among people to contraceptive hormones.
  + This is due to individual variation in receptor competency and level of endogenous hormone  production.
  + Remember, hormonal contraceptives are pharmacological agents, present at pharmacological  doses and in non-physiological temporal patterns.
    - Ex: the reason you don't get ovulation when you apply estrogen during a menstrual cycle at pharmacological doses and you give it everyday is b/c you are interfering with a process that allows FSH to initially stimulate follicle growth and you wont sense the increase in estrogen to stimulate the LH surge for ovulation.
    - Same thing occurs in the progestin only pills—there presence is in nonphysiological time patterns. You are taking the same amount of it each day at the same time across most of the cycle and then you take the sugar pills and you have no release. Basically you just have constant amount of the progesterone and that interferes with the process of normal menstrual function.
* Most of the side effects of oral contraceptives are due to E (this is why many women use progestin only contraceptives) but 40% of pill users have side effects of one kind or another. Below are those most commonly reported.
  + **Serious:**
    - Thromboembolism
    - Blurred vision
    - Loss of vision
    - Gallbladder disease—cholecystitis and gallstones
    - Hypertension
  + **Less Serious:**
    - Nausea - (alleviated by taking pill with dinner)
    - Weight gain, fluid retention, breast tenderness –b/c there are pharmacological amounts of estrogen in the system
    - Headaches
    - Depression, anxiety, fatigue, mood changes—looks like PMS—it is a circumstance in which you have excess sensitivity to E or insufficient P present to surmount antagonism to the E effects. Can be moderated by adjusting the dose of the pill (depends on what brand you are using)
    - Spotting, decreased menstrual flow
    - More yeast infections
    - Acne
* Progesterone side effects
  + Seen in P-only contraceptives
  + Most involve altered menses pattern
    - Heavy menses
    - Breakthrough bleeding
    - \*\*You can switch to different contraceptive or change dose
  + Multi-year implants can cause decreased ulnar bone density
    - So monitor individuals who are at risk for osteoporosis or that have calcium problems

**ESTROGEN-CONTAINING ORAL CONTRACEPTIVES AND CANCER**

* It is a misconception that the incidence of most reproductive system cancers is increased by using estrogen-containing contraceptives. It is variably affected. The risk is cancer-type specific and circumstance-specific as shown below.
* Cervical neoplasia risk ↑ up to 200%.
  + Appears to be due to ↑ intercourse in oral contraceptive users vs. nonusers so they have ↑ exposure of the cervix to pathogens/irritants etc.
* Breast cancer shows no increase or ↑ up to 200% depending on study.
  + Tamoxifen (E-receptor  blocker) decreases it but can increase risk of endometrial cancer. (Note: > risk increase than HRT  (26%).
* Endometrial cancer risk ↓ 10-80% (in nulliparous—women who have never had children).
  + Risk increased in multiparous (women who have had more than one child), unless P present in pill.
    - Safest if taken before age 51. (Note: HRT ↑ risk up to 100%).
* Ovarian cancer ↓ 10-60% (lowest occurrence in long time OC users).
* Note that a family history of a specific cancer-type generally moves an individual to the higher end of  the risk scale for that cancer type.

**EMERGENCY CONTRACEPTION**

* Strictly for pregnancy prevention after unprotected intercourse (not for routine use)
* Two major types
  + Copper IUD
    - 99% effective if inserted within 7 days of unprotected intercourse
  + Oral contraceptives in multiple doses
    - E+P type
      * Effective if started within 72 hours
      * 4-5 pills, (total of 150 μg ethinylestradiol + 2 mg Progestin) then repeat  in 12 hours
    - Progestin-only type (plan B)—
      * Effective if started within 48 hours
      * 2 pills, (total of 1.5 mg levonorgestrel), then repeat in 12 hours
    - For sexual intercourse occurring in the week before or after ovulation, treatment reduces  probability 75-88% (4 fold ↓ in risk of pregnancy)
* Other endocrine-based methods are not contraceptive, they cause abortion
  + Most common is Mifepristone (RU486, a P-receptor blocker) plus Misoprostol (prostaglandin—contraction of myometrium))

**ONGOING DEVELOPMENTS IN CONTRACEPTIVE METHODS**

* Mostly refinements in existing methods, to improve delivery and ease of use.
* The road to and through clinical trials is many years and many millions of dollars so progress is very  slow.
* Current efforts include:
  + **Female Contraceptives (all are vaccine-based)—these are all reversible** 
    - A) Specific antibodies against surface proteins on sperm or egg block sperm-egg binding needed for fertilization.
    - B) Specific antibodies against hCG prevent hCG roles in implantation and maintenance of corpus luteum.
    - C) Specific antibodies against GnRH shut down ovaries (requires hormone replacement)
    - General information for a), b), and c) above:
      * Route: Oral or injection
      * Efficacy: 95-100%
      * Side Effects: None demonstrated (except hormone replacement needed for c); potential for autoimmunity under study (they recommend this method isn’t used for >3 years w/o taking a year off)
      * Status: Anti-hCG vax in clinical trials, and others approaching clinical trials.
  + **Male contraceptives**
    - Adjudin (AF-2364)
      * Action: A less toxic relative of anticancer drug Lonidamine that disrupts sperm maturation (by breaking linkages between Sertoli cells and spermatids.)
      * Route: Patch or implant
      * Efficacy: 98-100%
      * Side Effects: none (covalent linking of Adjudin to FSH assures delivery only to testes)
      * Status: Approaching clinical trials
    - Askmen
      * Action: A synthetic progestin (Desogestrel) blocks spermatogenesis and T production (by inhibiting FSH/LH). T replacement required
      * Route: Pill
      * Efficacy: 100% (but does not work in 5-15% of men)
      * Side Effects: none with proper dose adjustment
      * Status: In clinical trials